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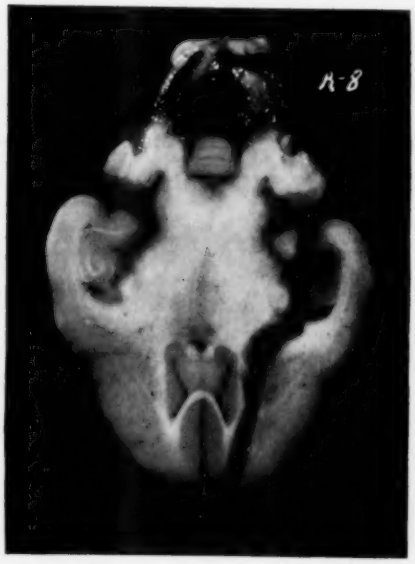

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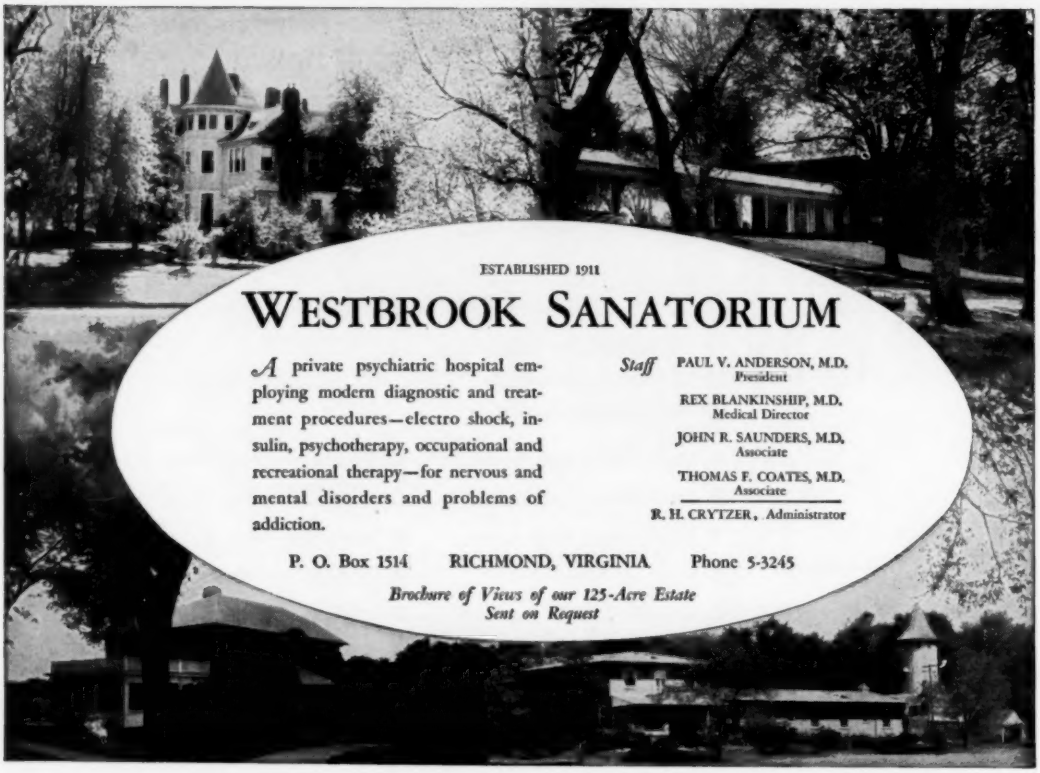
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Subarachnoid Hemorrhage Consequent to Intracranial Tumors

Review of Literature and Report of Seven Cases

BERNARD GLASS, M.D.
and
KENNETH H. ABBOTT, M.D., Columbus, Ohio

Not infrequently one hears discussed the possibility of subarachnoid hemorrhage occurring as an initial manifestation of intracranial tumor. Owing to the fact that spontaneous subarachnoid hemorrhage is most generally associated with intracranial aneurysms, this possibility (hemorrhage with brain tumor) too often is considered lightly and dismissed at the bedside. Because we had clinically encountered this condition more commonly than expected, we felt that the problem deserved further consideration; therefore, we undertook a survey of our cases and of the literature in order to define more accurately and clearly the clinical and pathological aspects of subarachnoid hemorrhage consequent to intracranial tumors. It was hoped that from this study we might better approach the problems of diagnosis and therapy in the presence of acute subarachnoid hemorrhage.

The medical literature on subarachnoid hemorrhage and brain tumors is extremely voluminous, and it has been impossible to review every paper. However, we have endeavored to cover the major portion of these cases, including those reported under various titles in which subarachnoid hemorrhage and brain tumors have existed. However, for the purposes of this paper we wish to emphasize that our primary interest in this study is those cases in which the onset of the clinical course was abrupt and mimicked in the main an acute spontaneous subarachnoid hemorrhage of the type seen with ruptured intracranial aneurysm.

In a study of 162 consecutive cases of intracranial tumors in our short series, we have had the good fortune to discover 8 in which the presenting problem was an apparent spontaneous subarachnoid hemorrhage. This relatively high percentage is more unusual in the light of autopsy studies such as those of Courville,* wherein subarachnoid hemorrhage was present in only 2 cases, in each caused by a glioblastoma, in a series of 50,000 necropsies at the Los Angeles General Hospital.

REVIEW OF LITERATURE

Historical Review.—In recent years subarachnoid hemorrhage has received considerable investigation,† and many reports have dealt with this subject, in all its ramifications. In earlier times, however, such reports with reference to either clinical or necropsy material were scarce. Jonathan Hutchinson [17] first diagnosed aneurysm (and subarachnoid hemorrhage) during life in 1863 (reported 1875). Earlier observations of the phenomenon of subarachnoid hemorrhage are known and recorded, but all too frequently these essays are vague, refer to autopsy cases, and have poorly documented references. Many of the earlier writers [5] discussed "meningeal" hemorrhage, in particular as it is related to aneurysms or trauma, but not always are the articles clear.

According to Hamby,[15] Brumi was the first to report an autopsy-proved case of

* Courville, C. B.: Personal communciation to the authors.

† References 10, 13, 23, 26, 27, 30, 31, 32, 34.

subarachnoid hemorrhage due to aneurysmal rupture—this was in 1778. Aneurysms per se were first recognized by Morgagni in 1761. In the English literature, Sir Gilbert Blane in 1800 reported the case in which bilateral aneurysm was found. The autopsy was performed by Hunter and Holme and witnessed by Blane and Jenner.[20]

It is interesting that Professor Klippel's [21] report on "meningeal hemorrhage," written in 1912, mentions "meningeal hemorrhage" reported by Paré (1517-1590) and Morgagni (1682-1771); however, Paré's case (that of Henry II) involved a traumatic subdural hemorrhage (Packard [28]) and is not within the province of our discussion. Klippel also knew of "meningeal hemorrhage" associated with brain tumor but was content to cover this possibility with one sentence.

In 1859 Gull [14] reported 62 cases (Dr. Brinton and colleagues) of subarachnoid hemorrhage with aneurysm. It is noteworthy that 28 of his cases involved the vertebral system.

Symonds [33] noted that the French author Gintrac also discussed meningeal hemorrhage in 1869. Scattered reports followed, such as those of Bramwell in 1886. Symonds' article, in 1924, finally gave more organized impetus to exploration of this subject in its various forms of appearance.

The less common causes of subarachnoid hemorrhage have received understandably less attention and discussion in the literature. However, it is apparent that these rarer causes are often surgically accessible lesions, and consequently their early detection may be life-saving for the patient. Among these less frequent lesions one may find intracerebral hematomas (due to various "vascular accidents") and many types of primary intracranial neoplasms, including vascular tumors, metastatic neoplasms, and pituitary tumors.

Case Reports from Literature.—During the 20th century some 22 authors have reported cases in which spontaneous subarachnoid hemorrhage was clinically associated with an intracranial tumor. This problem has been of interest to various investigators, some of whom have reported only autopsy material, while others have discussed clinical aspects.

Symonds' [33] report in 1923, with its discussion of 127 tumors and cysts, was among the very first in this category; however, the subarachnoid hemorrhage was associated with cysts (2 cases) rather than neoplasms. Five years later Bagley [1] and Bailey and Cushing [2] wrote concerning this matter; the former author reported subarachnoid hemorrhage in a 10-day-old infant, and the latter authors, two interesting cases of vascular tumor.

In 1932 Strauss and associates [32] cited a case of glioma, and Frank [12] discussed two vascular tumors in the German literature.

In 1937 Russell and Kershman [30] reviewed the literature and added three cases of their own. They discussed Schultz's [31] three cases, in which clinical data were insufficient to determine whether the cases belong here; also surveyed were three vascular tumors reported by Bergstrand, Olivecrona, and Tönnis,[3] but, again, no data were supplied.

During 1938 the French authors Beriel and Devic [4] found two examples in the category under discussion, and they cited two more described by Dechaume.‡ That same year Porta,[29] in Italy, had a most interesting report concerning a cerebellar lesion.

Jefferson,[18] in his presidential address in 1940, discussed (in part) this matter as it relates to the pituitary.§

Matera and Insausti [24] reported one case in 1946; Hesser [16] added three in 1948; Kirshbaum and Chapman [19] reported one more in the same year, and Bray,[6] another in 1949.

In the present decade, Echols and Rehfeldt [10] and Madonick and Savitsky [22] each had one case in 1951; Fountain and asso-

‡ Dechaume, M., reported by Beriel and Devic.[4]

§ Pituitary tumors are not often considered to be associated with spontaneous subarachnoid hemorrhage. Nürnberger and Korey [25] mention this as a possibility but cite no cases of their own. The review of the literature sheds interesting light on this concept of "pituitary apoplexy."

ciates [11] three more; Wolfe [34] and De Saussure and associates,[9] one each in 1953. In De Saussure's [9] case it is of interest that there were both a tumor and a vascular malformation present (not on the same side of the brain), and verified angiographically. Therefore, one cannot prove which of these two pathologic entities was responsible for the subarachnoid hemorrhage.

We now add eight cases of our own.

ANALYSIS OF REPORTED CASES

A total of 41 cases (from the literature and our own) have been found complete enough to be utilized for study. They form the basis for our analysis.

Surveys such as those of Oldberg [27] and Globus and Sapirstein [13] are of considerable interest but are based on autopsy material. Oldberg reviewed Cushing's 832 cases of glioma and found therein only 32 with hemorrhage, and in only 7 of these (0.84%) was the clinical history even suggestive of a possible spontaneous subarachnoid hemorrhage. Globus and Sapirstein [13] surveyed 94 autopsy cases without previous surgery, in order "to rule out surgery as a traumatizing agent." They made the interesting observation that "it is the exception rather than the rule for a tumor not to show some seepage of blood from its blood vessels into the surrounding tumor tissue." (However, the major portion of such cases did not give the clinical signs and symptoms of acute subarachnoid hemorrhage.)

Twenty of the above 94 patients had some evidence of bleeding in the cerebrospinal fluid. Nine of the patients had hemorrhage into a brain tumor. Of this group, only seven had lumbar punctures; of these only one had xanthrochromic cerebrospinal fluid (case of metastatic thyroid to brain). The vagaries of reporting and classifying such cases preclude our making a mathematically accurate analysis of all reported cases in this field.

Cerebrospinal Fluid.—In the reported cases hemorrhage has varied from slight (pink-tinged cerebrospinal fluid) to marked (grossly bloody). Subarachnoid hemorrhage has occurred in given cases from once to several times. Some patients have recovered after a single such episode, and in others the outcome has been fatal after either a single episode or multiple hemorrhagic episodes. Minimal bleeding occurred in six instances.‖ Moderate and nonfatal hemorrhage occurred in approximately 11 cases.¶ Fatal bleeding in the initial attack was found in three instances,[1] while multiple hemorrhages with fatal outcome were observed in the majority of reports.#

The exact number of hemorrhages could not be determined in all instances; but of 36 patients, 19 had more than one hemorrhage, 6 patients had one hemorrhage, 5 had two hemorrhages, 1 had three hemorrhages, 3 had four or five hemorrhages, 1 had six to eight,[10] and 1 had nine.[30]

Type of Tumors.—Of the 41 cases analyzed, primary gliomas of the brain accounted for 50% of the tumors (20 cases) causing the hemorrhage, with the following distribution: astrocytoma Grade IV, 11 cases *; astrocytoma Grade III, 1 case [9]; astrocytoma Grades I and II, 4 cases †; medulloblastoma, 1 case; oligodendroglioma, 1 case (Dechaume [4]); ependymoma, 1 case.[1] Primary melanoma [22] was found once; primary perivascular sarcoma (authors' case) occurred once.

Pituitary lesions (eosinophilic and chromophobic adenomas), surprisingly enough, occupy the second largest category, with 11 cases.‡

There were six vascular tumors, benign or malignant.§

There was a single cerebellopontine angle tumor [4] of unknown type.

Location of Lesion.—The tumor location did not seem to be related to the duration of

‖ References 4, 16, and 24.

¶ References 2, 4, 10, 11, 18, 24, 29, 32.

References 6, 7, 12, 16, 19, 22, 30.

* References 10, 16, 29, 30, 32.

† References 4, 24, 34. Dechaume, cited by Beriel and Devic.[4]

‡ References 7, 11, 18, and 19.

§ References 2, 6, 12, and 30.

symptoms or to the longevity following the onset of the acute phase. However, it is obvious that tumor location modified signs, symptoms, course, and rapidity of exitus. The majority of the lesions were supratentorial (34 cases). Of those tumors in the posterior fossa, one was an angle tumor,[4] two were in the fourth ventricle,[30] and five were in the cerebellar hemisphere.|| The sella turcica was involved 11 times.¶ Next in frequency was the right frontal lobe, with six tumors #; the right occiput, with three,* and the following locations with two each; left frontal,[16] left lateral ventricle,† left occiput,‡ and right temporo-occipital.§ In one instance the tumor was frontal (bilateral) and involved the corpus callosum[16]; in one case, frontotemporoparietal[22]; in one case primary in the corpus callosum,|| and in one case primary in the diencephalon. In one patient the glioma occurred in the left lateral ventricle.

Age Incidence.—The age range for 39 cases in which the age was known was from 10 days[1] to 70 years.[7] Bagley's 10-day-old patient with papillary ependymoma of the left lateral ventricle is the youngest patient reported in a case of this type; our youngest patient (Case 3) was 7 months old and harbored an astrocytoma Grade IV. Nine of the patients in the literature were 15 years of age or younger; of these, 6 were girls, 2 were boys, and for 1 the sex was not reported. In 38 cases the age is known. There were five cases in the first, third, and fourth decades; six in the second; nine in the fifth; four in the sixth, and three in the seventh.

Sex.—In 24 cases the sex was male; in 12 cases, female, and in 3 it was not reported.

Among the males of all ages, gliomas and pituitary tumor each occurred nine times; vascular lesions, five times; sarcoma once, and angle tumor once.

Among the females, gliomas occurred eight times; pituitary tumor, three times (one-third the frequency in the males); vascular lesions, twice, and primary melanoma, once.

On the basis of the date of report, there were nine survivors—one each in the first two decades¶; three in the third decade#; one in the fourth decade[2]; two in the fifth decade,[10] and one in the sixth decade.[11] Of the patients known to have died, 30 (100%) had necropsies.

The method of diagnosis in each case varied but in the main consisted of a history and physical examination (41 cases) and lumbar puncture (35 cases). The electroencephalogram was used on two occasions.[16] Seven of the patients were surgically explored.* One patient had an oil ventriculogram,[24] and three had air ventriculograms.† Pneumoencephalography was employed five times‡ and angiography sixe times.§

Signs and symptoms varied in this group, but it is interesting to note the following subjective and objective findings: Some type of headache occurred in 31 of the reported cases. In 19 cases a history of nausea and/or emesis was present. Nineteen patients had nuchal rigidity. Altered consciousness (lethargy, stupor, coma, etc.) was found 19 times. Eye signs of some type were a prominent feature and were observed in 27 instances. These ocular signs included diplopia, photophobia, decreased visual acuity, homonymous visual field defects, anisocoria, weakness of one or more extraocular muscles, and papilledema. In eight patients localized paresis or paralysis appeared, and in eight cases convulsions were observed. Olfactory hallucinations (or uncinate seizures) occurred in one case. Fourteen patients were found to have temperatures in excess of 100 F. Aphasia

|| References 2, 6, 12, 24, and 29.

¶ References 7, 11, 18, and 19.

References 9, 10, and 16.

* References 2 and 30.

† References 1 and 12.

‡ References 12 and 30.

§ References 16 and 32.

|| Dechaume, cited by Beriel and Devic.[4]

¶ References 2 and 24.

References 9, 11, and 18.

* References 2, 9, 11, and 25.

† References 1 and 2.

‡ References 9, 10, 16, 29, and 30.

§ References 9, 10, and 30.

Clinical Data on Eight Cases of Subarachnoid Hemorrhage Consequent to Intracranial Tumors

Case	Patient	Age, Yr.	Sex	Tumor and Location	No. of Clinical Hemorrhages	Symptoms	Onset of Symptoms to Death	CSF	Major Signs	Autopsy
1	H. K.	54	F	Astrocytoma, Grade IV, l. frontotemporal	1	Headache, olfactory hallucinations	2 mo.	Bloody, Grade IV	Coma, fixed pupils	+
2	W. S.	39	M	Astrocytoma, Grade IV, right frontal	2	Headache, dysesthesia fatigue of left arm	5 mo.	Bloody, Grade II	Hyperreflexia; bilat. Babinski; divergent squint, coma	+
3	D. D.	7 mo.	F	Astrocytoma, Grade IV, region left basal nuclei	1	?	2 days	Bloody, Grade IV	Restlessness, emesis, respiratory collapse; coma	+
4	M. C.	15	F	Glioma, left intraventricular	?	Headache, nuchal rigidity, diplopia	2 wk.	Bloody, Grade IV	None	+
5	J. H.	5	F	Medulloblastoma, fourth ventricle	12-15	"Sore neck and jaw"	1 mo.	Bloody, Grade IV	Emesis, general convulsions, bilat. Babinski, coma	+
6	R. A.	17	M	Perivascular sarcoma, right occipital	2	Headache	4 days	Bloody, Grade IV	Right hemiplegia; coma	+
7	F. A.	49	M	Chromophobe adenoma (clinical), pituitary	Multiple over 2 yr.	Loss of libido and potentia; severe headaches, chills, fever, and dysesthesia	2 yr.	Bloody and xanthochromic, Grade II	Sparse beard, large sella, nuchal rigidity	Still alive
8	G. M.	19	M	Cavernous hemangioma, right frontoparietal	1	Acute headaches	Several hours	Bloody, Grade IV	Grand mal, left Babinski, coma	+

occurred in one case. In no instance was the blood pressure (where reported) considered abnormal by the reporting authors!

REPORT OF CASES

Eight cases of intracranial tumor associated with subarachnoid hemorrhage are here reported. These cases are grouped according to histologic type, and not according to chronology (Table).

CASE 1 (H. K.).—A 54-year-old white woman was admitted to the hospital on Feb. 10, 1950, after being found unconscious at home. On admission, she was moribund and had fixed dilated pupils. A lumbar puncture disclosed Grade IV bloody cerebrospinal fluid, with a pressure in excess of 600 mm. of fluid. Twenty minutes after entering the hospital she died.

Two weeks prior to onset of present illness the patient had consulted a neurologist because she had had headaches and olfactory hallucinations for two months. Despite warnings about a tumor, she elected not to proceed with studies.

Upon opening the calvaria at necropsy, a bulging dura was seen on the left. When the dura was opened, a large amount of fresh blood was found beneath it and over the entire left cerebral hemisphere. A large clot was occupying the left frontal lobe and the ventricular system. Despite thorough inspection of the intracranial vessels, no aneurysm was found. Upon sectioning the brain, a grayish, infiltrating gliomatous mass was seen occupying the major portion of the left frontotemporal area. Histopathologic studies disclosed neoplastic glial tissue typical of a glioblastoma multiforme, in which there was an area showing extensive hemorrhage and necrosis of both tumor and brain. This occurred near the periphery of the tumor. The picture was that of an astrocytoma, Grade IV, of the left frontal lobe associated with brain degeneration and massive hemorrhage.

CASE 2 (W. S.).—On Oct. 6, 1947, one of us (K. H. A.) was requested to see a local hotel resident who could not be aroused after a drinking spree. The patient was vomiting and at times would become semiconscious and complain of headache. He had gone away from a party the previous evening after complaining of headache and nausea, and then he had emesis. He remained nauseous all night, vomited frequently, and complained of dizziness and left arm weakness. At 1 a. m. the hotel physician saw the patient and prescribed a sedative for "indigestion."

On the preceding June 4 (1947) this man complained of headaches and numbness of the left arm. Hospitalization at home failed to produce any diagnosis. Two months later he attended a midwestern clinic, where he was advised to have studies to exclude a brain tumor. This he refused to do.

His business associates soon noted that he was not his usual self; he seemed unable to keep up with his work and incapable of making quick decisions.

Examination on Oct. 6 revealed a 39-year-old white man, semicomatose, but able to respond to painful stimuli. His pupils were dilated but reacted. A spontaneous divergent squint appeared. The deep tendon reflexes were hyperactive, and a bilateral Babinski sign was present. The patient was moved to a hospital, and lumbar puncture showed the cerebrospinal fluid to be bloody, Grade II, and under a pressure of approximately 300 mm. of fluid. Conservative measures were instituted on the basis of a working diagnosis of subarachnoid hemorrhage secondary to an aneurysm. Forty-eight hours after admission the patient's condition became acutely worse, and the blood pressure rose to 240/80, followed by respiratory failure and death.

At autopsy, an egg-shaped cavity, 5 by 3 cm. in its greatest diameters, was encountered in the right frontal lobe. The cavity was filled with blood and yellowish necrotic material. The cavity lay within the white matter and made the right frontal lobe appear much larger than the left; the septum pellucidum was displaced to the left; the right lateral ventricle was not patent. Approximately 1.5 cm. posterior to its genu, the corpus callosum appeared necrotic, and numerous petechiae were found. No obvious neoplastic tissue was seen. The cavity had encroached upon the basal ganglia, without occupying them. Pontine and midbrain sections also contained many petechiae.

The diagnosis of abscess versus neoplasm was considered. Tissue taken from the periphery of the cavity showed a highly vascular neoplastic structure with anaplastic pleomorphism characteristic of glioblastoma multiforme (astrocytoma Grade 4).

CASE 3 (D. D.).—This is the case of a 7-month-old white girl who was admitted to the hospital in respiratory failure Jan. 15, 1952. She had been well until the afternoon of admission, when she had started to cry and be restless. At 6 p. m. she began to vomit. Her family physician saw her soon after and performed a lumbar puncture. The fluid was bloody. Respiratory failure occurred as she was being carried into the hospital. The ventricles were tapped at once; the fluid was grossly bloody. Despite all attempts to save her, she died after 48 hours in a respirator.

Subsequent postmortem examination revealed a 960 gm. brain with flattened convolutions and obliterated sulci. Careful inspection of the base of the

brain failed to produce evidence of aneurysm. On section, a large left cerebral tumor was observed. This measured 8 by 9 cm. and was an astrocytoma Grade IV.

CASE 4 (M. C.).—A 15-year-old white girl, three weeks and three days after birth of a premature infant, had the sudden onset of headaches, stiff neck, and diplopia. There were no localizing neurological signs.

A lumbar puncture was performed, and the spinal fluid pressure was found to be over 500 mm. of water and was grossly bloody, with xanthochromia. There were 8 white blood cells per high-power field. The protein was 358 mg., and the sugar 65 mg., per 100 cc.

She was hospitalized on Aug. 25, 1954. Her neurological examination suggested the possibility of a left frontal lesion. A left carotid angiogram revealed a wide-sweeping, elevated left anterior carotid artery and a suggestion of a tumor stain in the left frontoparietal area.

The ventriculogram showed a dilated, blocked left lateral ventricle containing xanthochromic fluid with 1154 mg. of protein per 100 cc. A definite mass was seen in the left lateral ventricle, and on craniotomy an intraventricular glioma was found occupying the major portion of the body and the anterior horn of the left lateral ventricle. The tumor extended through the foramen of Monro into the third ventricle. It was removed successfully.

Her immediate postoperative course was uneventful, until she suddenly became comatose on the second postoperative night and developed dilated, fixed pupils. She died in a few hours, consequent to a pontine hemorrhage.

CASE 5 (J. H.).—A 5-year-old white girl was admitted to the hospital on Feb. 19, 1953, because of generalized convulsions, followed by coma. One month prior to admission she started to have emesis every other day; between the bouts of emesis she felt well. Two days prior to admission she complained of "sore neck and jaws" and vomited eight or nine times. This was followed the next day by difficulty in seeing and hearing. The past history was not contributory. Admission examination revealed a fairly well-developed, thin, comatose white female child with elevated temperature (100 F [rectal]), tachycardia (100) tachypnea (34), and systolic pressure of 90 mm.

On neurological examination there was found sluggish pupillary reaction, bilateral recent retinal hemorrhages without papilledema, Grade IV nuchal rigidity, hyperactive tendon reflexes, and a bilateral Babinski sign. Lumbar puncture was easily performed; the cerebrospinal fluid was grossly bloody (12,250 RBC per cubic millimeter). The urine contained 2000 mg. of albumin per 100 cc. Supportive treatment was instituted on admission but proved of no avail, and the child died within three hours.

At necropsy the brain appeared edematous but not otherwise noteworthy on the surface. A globular blood clot was found in the fourth ventricle. Histologic sections through the clot revealed tissue characteristic of medulloblastoma.

CASE 6 (R. A.).—A 17-year-old white boy had been swimming with some friends. He left the water to pose on a rock for a photograph, when he suddenly slipped (?) and fell, striking his head (?). He was unconscious for a few seconds. For the next four days he complained of headache, and then late in the fourth day cried out with sudden excruciating head pain and fell unconscious. On arrival at the hospital a few minutes later he was in deep coma. He had a dilated right pupil and right hemiplegia.

A lumbar puncture showed grossly bloody (Grade IV) cerebrospinal fluid with a pressure well in excess of 600 mm. of fluid. The patient was taken to surgery, and multiple burr holes disclosed a large right occipital intracerebral clot. Careful inspection of the adjacent brain enabled us to find a small bit of grayish-red friable tissue which was saved for histologic study. The patient lived only a few hours after operation.

Autopsy failed to disclose either aneurysm or tumor. The right occipital lobe was almost completely destroyed by the hemorrhage, which had extended into the parietal and temporal lobes. Sections of the small biopsy specimen showed a typical perivascular sarcoma (a primary intracerebral tumor).

Comment.—This is the only perivascular sarcoma of the brain in our series of 162 intracranial tumors. This sarcoma and the glioblastoma in Case 1 had suffered the same extensive, nearly total, destruction consequent to massive hemorrhage within its substance.

CASE 7 (F. A.).—This patient, a 49-year-old white man, a politician, was seen in consultation on Nov. 6, 1953, because of severe frontal headache. He had noted sporadic headaches over the past two years, and these occasionally required bed rest for relief. He had a long history of "nervous stomach," tension states, and irritability. Early in the morning of the day prior to admission, he awakened with severe transfrontal cephalalgia, which was accompanied by nausea and vomiting.

Consciousness was unclouded in the face of progressive pains, which became lancinating and were aggravated by cough, sneeze, and strain. Soon the patient developed chills with fever and paresthesiae in both arms. The past history was note-

worthy because of marked decrease in libido and potentia not consistent with aging alone.

On physical examination this man appeared acutely ill and restless. His temperature was 98.6 F; respirations, 20 per minute; pulse, 80 per minute, and blood pressure, 120/80. Physical and neurologic examinations were not unusual except for nuchal rigidity and sparseness of his beard. Cerebrospinal fluid was bloody (Grade II xanthochromia) and under increased pressure. Chest x-rays were negative, but skull x-rays showed a large, ballooned-out sella with thin posterior clinoid processes. The clinical impression was subarachnoid hemorrhage secondary to chromophobe adenoma of the pituitary. Bilateral carotid angiograms disclosed the usual amount of displacement of the carotid arteries and upward displacement of the anterior cerebral arteries, consistent with the clinical diagnosis.

A program of conservative therapy was outlined and followed, with success so far. Deep x-ray therapy was given via temporal and frontal portals, and the patient was dismissed with hormone substitution therapy. At present this patient's panhypopituitarism is compensated, and he is being followed as an outpatient.

Case 8 (G. M.).—A 19-year-old white youth was admitted, comatose, to the hospital emergency room, on Nov. 8, 1950. His fellow workers reported that he was seized with sudden occipital pain while at work. He complained of dizziness, then immediately lost consciousness. The patient was hospitalized at once. No previous history of disease was given.

Examination showed that the right pupil was dilated and the left constricted; there was bilateral absence of light reflex. The patient appeared decerebrate, and a strong left Babinski sign was present. Blood pressure was 80/60, and the pulse was 110 per minute. A lumbar puncture revealed the cerebrospinal fluid to be grossly bloody (Grade IV) with a pressure above 600 mm. of water. The patient had several grand-mal-like seizures and died two hours after admission.

At autopsy no evidence of head injury was found. Subarachnoid hemorrhage was limited to the posterior portion of the brain and interhemispheral area, as well as the base. Careful dissection of the circle of Willis disclosed no evidence of aneurysm.

After fixation, the brain on coronal section revealed several widely dilated blood vessels situated immediately behind the anterior tip of the right frontal lobe. These vessels were surrounded by a massive clot. In one margin of this area was an extensive cavity which extended back into the frontal lobe and anterior portion of the parietal lobe. This cavity, as well as the ventricles, contained a massive blood clot.

Representative sections from the above areas disclosed a large number of dilated, thin-walled blood vessels, typical of a cavernous hemangioma, into and from which extensive fresh hemorrhage had occurred.

Comment on Our Cases.—An analysis of the cases we have personally studied and are presenting here reveals the age range to be from 7 months to 54 years. Of the eight cases (gliomas and other tumors) four were males and four females. Four of these patients had clinical evidence of more than one subarachnoid hemorrhage. Two of the gliomas occurred in female children (7 months and 5 years). Three of the five glioma patients were females. Of these cases, astrocytoma Grade IV accounted for four and medulloblastoma for one.

There was one case each of perivascular sarcoma, pituitary adenoma, and cavernous hemangioma.

Only one patient survived (Case 6)—a man with a pituitary tumor.

Excluding the one survivor (Case 6), we find that the average life span from known onset to death was approximately 49 days—the shortest being several hours (Case 7), the longest 5+ months (Case 2).

Tumor locations varied but were primarily frontal (Cases 1, 2, 3, and 8), with one tumor occipital (Case 6), one in the fourth ventricle (Case 5)—the only infratentorial tumor—one in the left lateral ventricle (Case 4), and one in the pituitary (Case 7).

Headache as a major complaint occurred with certainty in six of the cases (Cases 1, 2, 4, 6, 7, and 8). In addition, complaints of hallucinations (Case 1), dysesthesiae (Cases 2 and 6), fatigue (Case 2), "sore neck and jaw" (Case 4), and chills, fever, decreased libido, and potentia (Case 6) were noted.

At the time of hospital admission all the patients, except the one survivor (Case 6) and Case 4, were in coma, with varying degrees of paralyses, ocular signs, and stiff neck.

Bloody spinal fluid was present in all eight patients. Autopsies were performed on the seven patients who died.

GENERAL COMMENT

This small series does not lend itself to statistical analysis, but a few comparisons seem of interest.

A comparison with aneurysms (in a general way) shows the high correlation of headache, emesis, stiff neck, bloody spinal fluid, and eye signs from a clinical standpoint. The age group also shows cases outside the usual range for aneurysm (Cases 3, 4, 5, and 7). Hamby [15] cites Dandy's figures showing that few cases of aneurysm are to be found below the age of 20.

On the basis of autopsy figures, aneurysms are estimated to occur in from 0.5% to 1% in the general population (Hamby [15]). It is most difficult to estimate a similar figure for neoplasms and subarachnoid hemorrhage, but in our present series this group represents approximately 4.9%.

With reference to longevity there are various figures, but Hamby [15] cites cases of survival of from one month to eight years following an attack. Approximately one-third of his patients died in the initial major attack, whereas one gathers this figure would be much higher on an over-all basis when subarachnoid hemorrhage has its origin in a tumor.

Treatment of the two entities cannot be discussed point for point in this paper, but it is apparent that if the mortality figures are to be lowered in the tumor group, rapid surgical therapy must be instituted. Unfortunately, for a variety of reasons, patients do not always come to seek neurosurgical aid at propitious moments, and thereby the opportunity to help them slips away.

MECHANISMS OF HEMORRHAGE

The mechanism of hemorrhage in these cases would seem to be the same as that for hemorrhage into most malignant gliomas. Vascular endothelial proliferation with subsequent obliteration of the lumen of the vessel, as a cause of necrosis and subsequent hemorrhage into the tumor, is a commonly observed condition in glioblastomata, as well as in other highly malignant neoplasms. Thin-walled, poorly formed vessels in a tumor may also become distorted with growth of the tumor, and these may easily rupture and hemorrhage. Necrosis, with subsequent loss of vessel support, may be a factor in production of hemorrhage. Tumor erosion of vessels is another probable cause.

The reasons for such infrequent association of clinical subarachnoid hemorrhage with brain tumor may be the result of several factors, among which are lack of examination of the cerebrospinal fluid at an appropriate time, paucity of thin-walled or necrosing vessels on or in the tumor which present in or near a subarachnoid or ventricular surface, surgical intervention in many cases prior to the time at which a hemorrhage would have occurred, and lack of adequate neurological studies in some cases, making absence of hemorrhage seem commoner.

The causes for death in these cases are quite obviously due to the usual factors of increased intracranial pressure, shifting of the midbrain, etc., and consequent midbrain and pontine hemorrhage.

The prognosis in the majority of cases would seem to be poor, particularly since most such patients are seen by the neurosurgeon some time after the hemorrhage has accomplished its fatal mischief. All too frequently the hemorrhage is merely one of many symptoms that have gone too long, without proper analysis, recognition, and definitive therapy. The majority of the tumors causing subarachnoid hemorrhage are highly malignant, though at times the reports are not clear as to histologic types; hence the survival rates in such instances are not good, regardless of hemorrhage. For those who take a pessimistic view of our inadequate therapeutic modalities for the malignant gliomas, it would seem that such fatal hemorrhages serve well to avert a needless craniotomy and its blood-letting pseudotherapeusis!

There is, however, a brighter side which needs emphasis. There are some "benign" lesions, such as those of the pituitary; there are some circumscribed benign vascular lesions, and surely there must be some less

highly malignant gliomas which would have good survival rates if discovered early.

In the main, the problem requires close cooperation of all concerned: the patient, family physician, emergency room physician, neurologist, and neurosurgeon. Knowledge of the facts, a high index of suspicion, and ability to carry out a decisive and reasonable action will all help toward raising, in some measure, the survival rate in this group, as well as in other neurosurgical groups of problems.

SUMMARY

A series of eight cases of spontaneous subarachnoid hemorrhage secondary to intracranial tumors are described.

The literature is reviewed, and the low incidence of reports in the past 53 years is noted. Forty-one cases, including citation of the authors, are reviewed.

The glioma group is the largest single group of all case reports in both the surgical and the necropsy material—20 gliomas, or 48.7%.

Children are rarely involved in cases of this type. Two examples are described.

The clinical and pathologic aspects of subarachnoid hemorrhage in the presence of brain tumors are discussed. Attention is given to the mechanism of such hemorrhages.

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News and Comment

GENERAL

Epileptics Anonymous.—Epileptics Anonymous, patterned after AA, has been established in Los Angeles, where there are over 25,000 epileptics in the county. In the three weeks since its formation seven active groups have begun holding regular weekly meetings, and all indications point to a rapid spread of the organization across the country. It is estimated there are 1,500,000 epileptics in the United States, making this the third most prevalent disorder in the nation.

Members of the new Epileptics Anonymous groups have found that the EA program and principles offer them the same haven of hope, understanding, and mutual help that the Alcoholics Anonymous program has so successfully offered the alcoholic during the last 20 years. The EA program is, in fact, merely an adaptation of AA to fit the specific needs of the epileptic. EA offers no miracle drug or "cure" for epilepsy, but does offer through its "Twelve Steps" a suggested program of self-help for the epileptic who wants it, to be practiced as he desires to fit his individual need.

Epileptics Anonymous has no dues or fees. It is not allied with any sect, denomination, organization, or institution. It is not organized as a business. Any epileptic may start an EA group anywhere. The only requirement for membership is a desire to help themselves through helping other epileptics. Complete information about Epileptics Anonymous may be obtained by writing to P. O. Box 75532, Los Angeles 5.

SOCIETY NEWS

Canadian Neurological Society.—The Canadian Neurological Society will hold its Seventh Annual Meeting in Toronto on June 16-19, 1955. After this, on June 20-24, the British Medical Association is meeting conjointly in Toronto with the Canadian Medical Association and the Ontario Medical Association.

Blood-Brain Barrier and Ground Substance of Central Nervous System

Similarities in Development

ARTHUR HESS, Ph.D., St. Louis

In the gray matter of the adult central nervous system, a homogeneous positive periodic acid-Schiff reaction occurs in the spaces between the cells, dendrites, axon terminations, and neuroglia fibers. On the basis of histochemical tests, this reaction has been ascribed tentatively to the presence of a neutral mucopolysaccharide (Hess,[10] 1953) and has been regarded as demonstrating an intercellular ground substance of the adult central nervous system. The existence and finding of this reaction prompted the suggestion that "the presence of a ground substance of a carbohydrate-protein nature might well deserve attention when considering the problem of the penetration of substances into the central nervous system and the properties of the blood-brain barrier" (Hess[10]).

In an attempt to test this hypothesis, experiments were performed correlating the time of appearance of the ground substance of the central nervous system and the development of the blood-brain barrier.

The ground substance is best revealed by periodic acid-Schiff staining (Hess[10]). A review of the literature (King,[12] 1939) demonstrates that trypan blue is a valid test substance for the demonstration of a blood-brain barrier. When trypan blue, administered intravenously or intraperitoneally, does not stain the brain, the blood-brain barrier is present. Presence of trypan blue staining and absence of blood-brain barrier are also related.

The central nervous system of adult animals does not store trypan blue, presumably because of the presence of the blood-brain barrier. The central nervous system of several neonatal and immature forms, on the other hand, does indeed store trypan blue (Behnsen,[2] 1927; Stern and Peyrot,[15] 1927; Penta,* 1932), presumably because of the absence or lack of development of the blood-brain barrier in these young animals. More recently, Bakay[1] (1953), using radioactive phosphorus in rabbits, has confirmed these results and has shown that the permeability of the blood-brain barrier is greater in the fetus and the young animal than in the adult.

Behnsen[2] showed that the storage of trypan blue in mice is less at the age of 3 to 5 weeks than at 1 to 2 weeks and considerably less after the age of 5 weeks. It now remains to correlate the presence of the ground substance of the central nervous system with the ability of the mouse brain to store trypan blue.

METHOD

The brains of 32 mice, varying in age from newborn to 22 days, and of one mouse of 35 days were removed and fixed in Rossmann's fluid (absolute alcohol saturated with trinitrophenol, 90 ml.; 40% solution of formaldehyde U. S. P., 10 ml.). Paraffin sections 15μ in thickness were prepared and stained

From the Department of Anatomy, Washington University School of Medicine.

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* Penta,[13] cited by King[12] and Spatz.[14]

by the periodic acid-Schiff (PAS) technique, as previously described (Hess[10]). Four mothers of the young mice were also used to compare the distribution of the PAS-positive substance in the brains of these animals with that in their offspring.

RESULTS

The distribution of the PAS-positive ground substance in Rossmann-fixed paraffin sections of the brain of the adult mouse is as previously described (Hess[10]). The white matter is uncolored, whereas a light-red coloration is disposed evenly in the gray matter between the unstained nerve cells (Fig. 1).

Reaction of the Ground Substance of the Mouse Brain to the Periodic Acid-Schiff (PAS) Procedure

Age, Days	No. of Animals	PAS Staining of Ground Substance
Adult	4	+++
Newborn	4	0
1	1	0
2	1	0
3	2	0
4	1	0
5	2	+, 0
6	1	+
7	1	+
8	1	++
9	1	++
10	2	++
11	1	++
12	1	++
13	2	++
14	1	+++
15	1	+++
16	2	+++
17	1	+++
18	2	+++
19	1	+++
20	1	+++
21	1	+++
22	1	+++
35	1	+++

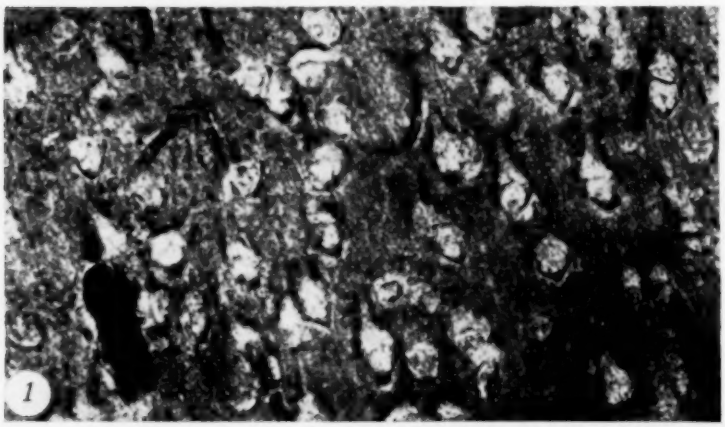
The occurrence of the ground substance in the cerebral cortex was studied. Young mice exhibit glycogen in the brain after PAS staining. The newborn mouse has relatively large amounts of glycogen, which occurs in ever decreasing amounts until about 10 days of age, after which it essentially is not revealed in most of the gray matter by the present techniques. The ground substance of some of these animals was studied after removing the glycogen by saliva digestion, which has no effect on the ground substance.

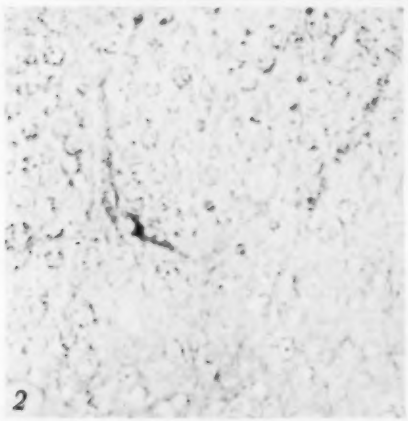
The results are presented in the Table. The amount of ground substance and the approximate degree of intensity of reaction to the PAS procedure have been rated from 0 to 3+. The thickness of sections and the staining procedure have been standardized as far as possible. Although the ratings have been assigned by the subjective impression gained by visual examination, the results have been quite consistent and indicate that the time of appearance and increase in quantity of the ground substance can be readily determined.

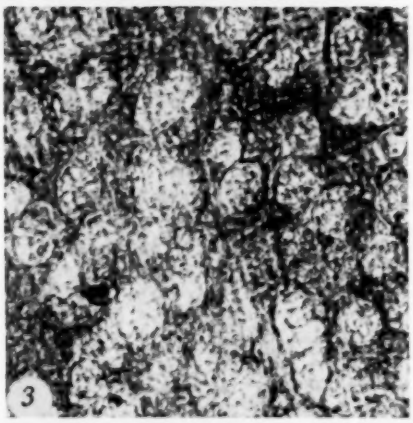
In the newborn animal the ground substance is absent (Fig. 2). The cells of the cerebral cortex are close together, so that intercellular spaces are essentially lacking. In the one-day-old mouse the ground substance is still absent, as are large intercellular spaces. In the 2-day-old mouse intercellular spaces appear, and increase in size in the 3-day-old animal. By 4 days of age the intercellular spaces are relatively large. However, in all these animals up to 4 days of age, the spaces between the cells, large or small, are PAS-negative, and the ground substance has not appeared.

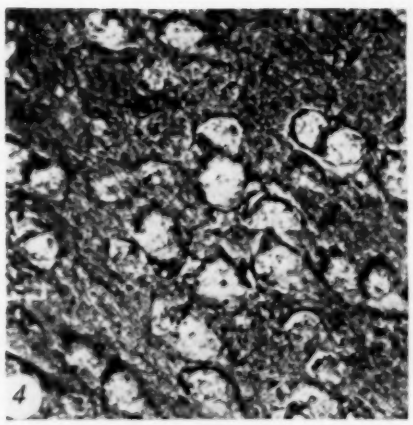
At 5 days of age the ground substance begins to make an appearance. The spaces between the cells of one of the animals examined at this age revealed a slight pink color after the PAS procedure. The intensity of the reaction was weak because of the small intercellular spaces and the actual light color assumed by the ground substance. In the other mouse examined at 5 days of age the ground substance was still negative. At 6 and 7 days of age the ground substance stains in a faint, but definite, fashion (Fig. 3). Thus, toward the end of the first week the ground substance initially appears in the cerebral cortex of the mouse and is rated 1+.

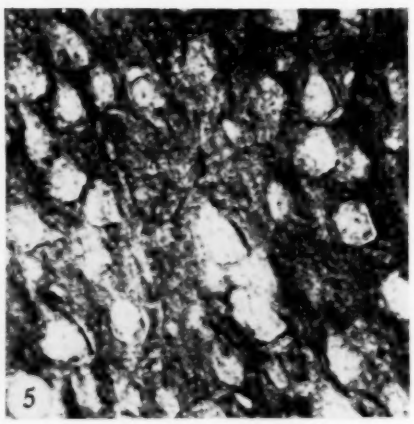
At 8 days the ground substance has increased in amount and stains more intensely than before (Fig. 4). The cells also become separated by larger intercellular spaces. This











Figs. 1-5.—Sections of cerebral cortex of the mouse; paraffin sections, periodic acid-Schiff procedure; × 580.

Fig. 1.—Adult mouse. The ground substance is colored pink and evenly distributed between the unstained cell bodies. Blood vessels are stained red.

Fig. 2.—Newborn mouse. Staining of ground substance: 0.

Fig. 3.—Six-day-old mouse. Staining of ground substance: +.

Fig. 4.—Eight-day-old mouse. Staining of ground substance: ++.

Fig. 5.—Fourteen-day-old mouse. Staining of ground substance: +++.

condition of the ground substance remains essentially the same until 13 days of age. Thus, during the second week of life the ground substance in the mouse cerebral cortex increases in amount and in intensity of staining, and is rated 2+.

At 14 days of age the ground substance increases markedly in intensity of staining and in amount (Fig. 5). On the whole, after 14 days of age the picture presented by the ground substance after the PAS procedure is similar to that of the adult. The size of the intercellular spaces is also like that of the adult. Thus, after two weeks of life, the ground substance appears similar in amount and in intensity of staining to that of the adult and is rated 3+.

These experiments show that there is a correlation between the decrease in ability of the mouse brain to store vital trypan blue after 2 weeks of age (Behnsen [2]) and the appearance and assumption of adult proportions by the ground substance at this time. This correlation is not exact, since the storage of trypan blue by the mouse brain continues to decrease after 3 weeks of age, and even after 5 weeks of age (Behnsen [2]), while the ground substance has already assumed adult proportions at 2 weeks of age. However, this is probably because quantitative estimates of the ground substance are roughly made, and procedures have not yet been developed which can reveal qualitative or quantitative differences between the ground substance in the brain of a 2-week-old mouse and that of an adult.

The development of the ground substance in the mouse brain is relatively constant when compared with that of the guinea pig (Hess,[11] 1955), which exhibits several individual variations in amount of ground substance from the time of its initial appearance to its achievement of adult proportions. The histochemical reactions of the ground substance in both mouse and guinea pig brains are similar. Although a detailed study of this point was not undertaken, the ground substance seems to make its appearance at the same stage of development throughout all parts of the brain. The development of the PAS-positive intercellular matrix in the thalamus and in the cornu Ammonis appears similar to that of the cerebral cortex.

COMMENT

The site of the blood-brain barrier has been said to reside in the cerebral capillaries, in the capillary endothelium, or in the piaglia membrane. From the results of the present experiments, it seems that the ground substance of the central nervous system contributes to the blood-brain barrier and is a substance which prevents the staining of the adult normal brain by trypan blue.

Previously unknown to me, but recently discovered in the literature, are the experiments of Bouton [3] (1940), who also correlated the presence of a ground substance and the ability of trypan blue to stain the brain. Taft [16] (1938) had previously acknowledged the presence of an intercellular substance in the central nervous system and attempted to cite illustrations of its importance. Bouton,[3] using these results and revealing the so-called intercellular substance by the Bodian method, created air emboli in the brains of dogs and then injected trypan blue. He claimed that the air emboli caused destruction of the intercellular substance, with a minimal damage to the blood vessels and other formed elements. In places where the intercellular substance disappeared, the trypan blue entered the brain. Although cleverly conceived, his experiments are still subject to adverse criticism. Inflammation and necrosis of nerve tissue permit vital staining of the brain (King [12]). It is impossible to eliminate inflammation and some necrosis of nerve tissue when injecting air into the vascular system and creating air emboli in the blood vessels of the brain. The air emboli might well cause necrosis of the capillary endothelium, permitting trypan blue to enter the brain by exudation through the injured blood vessels. Indeed, Broman [4] (1940) found that air emboli caused such changes and that trypan blue did stain brains so treated. Nevertheless, Bouton's [3] (1940) conception that the intercellular substance of the central nervous system is an essential

factor of the blood-brain barrier appears valid. The use of young animals where the blood-brain barrier and the ground substance of the brain are not yet developed provides support to this theory.

Trypan blue, administered intravenously, does not succeed in staining the brain of adult animals. However, subarachnoid injection of trypan blue in adult animals stains the brain freely (Goldmann,[9] 1913). This has led to the conclusion that the site of the blood-brain barrier is in the capillary endothelium of the central nervous system (Spatz,[14] 1933). Successful staining of the brain by subarachnoid injection of trypan blue raises a serious objection to the concept that the ground substance contributes to the constitution of the blood-brain barrier. With subarachnoid injection of trypan blue in adults, the ground substance is present and might perhaps be expected to block the staining of the nerve elements. However, King [12] and Friedemann [8] (1942), although the latter is one of the supporters of the theory that the capillary endothelium is the locus of the blood-brain barrier, have presented extensive, logical objections to this line of argument and have justifiably made the point that the results of subarachnoid and intravenous injections of trypan blue or other substances are not comparable. It is not attempted to say here that the ground substance is the sole site of the blood-brain barrier. The answer to the fate of any substance after intravenous administration must, of course, involve the capillaries and the permeability of their walls. The use of the term "blood-brain barrier" implies a realization of the fact that the vascular channels must enter significantly into any consideration of the elements that govern entrance and exit of substances into and out of the brain. Indeed, consideration of the permeability of the capillary wall should also involve consideration of the characteristics of the other elements on either side of this wall. Thus, it is, rather, suggested here that the blood-brain barrier is formed by the walls of the brain capillaries (endothelium and/or pia-glia membrane) plus the ground substance plus the elements of the brain itself. However, the ground substance is the significant variable factor, whose absence or presence determines the presence or absence of the ability of intravenously administered trypan blue to stain the brain and the absence or presence of the blood-brain barrier.

King [12] postulated a concept of "affinity," purporting to explain the lack of staining of the brain by intravenous trypan blue. He suggested that the brain lacks "certain unknown factors" by which trypan blue is bound and rendered available to the tissue. He also suggested that this unknown factor might be connective tissue. In his opinion, trypan blue has a specific affinity for connective tissue, which is absent from most of the brain. It is suggested here, as was also mentioned by Bouton,[3] that it is the ground substance that represents the previously unknown essential factor that permits or inhibits trypan blue staining of the brain.

The conception that the ground substance of the central nervous system is an integral part of the blood-brain barrier aids in explaining results that have heretofore presented puzzles. The brains of newborn guinea pigs do not store sodium ferrocyanide, which can also be used as a test agent for the presence of a blood-brain barrier (Stern and Peyrot [15]), nor can they be stained by intravenous trypan blue (Broman,[5] 1941). This is exceptional, since the brains of neonatal mice (Behnsen [2]), rabbits (Stern and Peyrot,[15] Penta †), cats (Stern and Peyrot,[15] Penta †), rats (Stern and Peyrot [15]), and dogs (Stern and Peyrot [15]) do indeed store sodium ferrocyanide and trypan blue and hence do not have a blood-brain barrier. Hess [11] has shown that the ground substance of fetal guinea pig brains makes its appearance at about 45 days' gestation age, increases in amount, and by 50 days of gestation is similar in appearance and quantity to that of the adult. Therefore, the brain of the newborn guinea pig already has ground substance and a blood-brain barrier and hence resists vital staining. The absence of this ground substance and the consequent

† Penta,[13] cited by King [12] and Spatz.[14]

absence of the blood-brain barrier in the other neonatal forms mentioned permits the vital staining of the brain by trypan blue.

The guinea pig brain at birth is relatively mature. Cerebral cortical activity and the ability of the cortex to evoke muscle contraction develop suddenly in the prenatal guinea pig (Flexner,[7] 1952). There is a more gradual development of electrical activity in the postnatal rat, cat, and rabbit (Crain,[6] 1952). It is interesting to note that the presence of the ground substance of the brain, the consequent presence of a blood-brain barrier, the morphological and chemical maturation of neurons, and patterns of electrical activity appear simultaneously in the fetus or young animal and undergo a parallel subsequent history during the development and maturation of the nervous system.

SUMMARY AND CONCLUSIONS

The brains of mice, varying in age from newborn to 35 days, were stained by the periodic acid-Schiff (PAS) technique. Occurrence of the PAS-positive ground substance in the cerebral cortex was noted and a rating assigned to the amount and intensity of staining of this substance (Table). The ground substance is not present in the cerebral cortex of neonatal mice and is absent for four days of life. At 5 days of age the ground substance makes its appearance, continues to increase in amount, and becomes similar in proportion to that of the adult brain at 14 days of age. This appearance and increase in amount of the ground substance are correlated with the development of the blood-brain barrier and the ability of the mouse brain to stain with intravenous trypan blue. The mouse brain stains easily and extensively with trypan blue until 2 weeks of age, when the storage of vital trypan blue begins to decrease. The brains of newborn mice store vital trypan blue; the ground substance is absent in neonatal mice. Therefore, the presence or absence of the blood-brain barrier, as tested by the absence or presence of trypan blue staining, is somewhat correlated with the presence or absence of the ground substance of the central nervous system. Confirmation is given to this theory by the observation that the brain of the newborn guinea pig resists vital staining and already has a blood-brain barrier. The ground substance of the central nervous system makes its appearance and assumes adult proportions in the guinea pig fetus, so that the neonatal guinea pig already has ground substance in the central nervous system. The conclusion is reached that the ground substance of the central nervous system contributes to the constitution of the blood-brain barrier and is the substance responsible for the ability of normal adult brain to resist vital staining by trypan blue.

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News and Comment

ANNOUNCEMENTS

Course in Neuromuscular Diseases of Children.—A course in the Neuromuscular Diseases of Children with Special Emphasis on Cerebral Palsy will be offered by Dr. Meyer A. Perlstein at the Cook County Graduate School of Medicine, in Chicago, beginning June 20, 1955. This is an intensive two-week didactic and clinical course in the diagnosis and management of the neuromuscular diseases of children with special emphasis on cerebral palsy, and includes field trips to itinerant clinics. Tuition for the course is $225.00, which includes the costs of luncheons during the course and the cost of transportation and hotels during itinerant clinics. Registration, which is limited, may be made by applying to the Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago.

American Academy for Cerebral Palsy.—The Annual Meeting of the American Academy for Cerebral Palsy will be held in Memphis, Oct. 10, 11, and 12, 1955. The meetings are open to members of the medical and allied professions who are interested in cerebral palsy. The three-day program will include instructional courses in the various phases of cerebral palsy, as well as a formal program. Those wishing to attend may obtain an invitation from Robert A. Knight, M.D., secretary-treasurer, upon request; hotel reservations are to be made directly with Mr. Scott Stewart, manager of the Claridge Hotel, Memphis, convention headquarters. Dr. Lenox D. Baker, Duke Hospital, N. C., is president of the organization.

American Neurological Association.—The 80th Annual Meeting of the American Neurological Association will be held at the Palmer House, Chicago, June 13-15, 1955.

Alerting Responses and Actions of Atropine and Cholinergic Drugs

FRANCO RINALDI, M.D.
and
HAROLD E. HIMWICH, M.D., Galesburg, Ill.

A survey of the literature on the action of acetylcholine (ACh), anticholinesterase drugs, and atropine suggests that these substances influence the neuronal mechanisms involved in the production of the diffuse desynchronization of the electrical activity of the brain, also known as the arousal, or activating, or alerting response.[1] Bonnet and Bremer * observed that small amounts (0.2γ to 2γ) of ACh chloride, in intracarotid injections, "awakened" the *encephale isolé* cat preparation. Wescoe and associates [4] reported that isofluorophate (diisopropyl fluorophosphate; DFP), a powerful anticholinesterase synthetic substance, diminishes the voltage and increases the frequency of the dog EEG activity, while atropine, on the contrary, raises the voltage and shifts the frequency to the slower side, thus counteracting the isofluorophate-induced changes. Funderburk and Case [5] showed that in cats and monkeys atropine induces EEG changes identical with those of natural sleep (high-voltage slow waves and bursts of 10 to 14 c/s spindles). They also observed that if the dose of atropine was large enough (1 to 2 mg/kg.), it was extremely difficult to elicit an alerting reaction, despite the fact that the animal was behaviorally awake. On the other hand, the same authors reported that physostigmine produces the opposite effect, with a permanently alert (low-voltage fast activity) EEG pattern.

Similar observations with atropine were made by Wikler [6] in unrestrained dogs with permanently implanted dural electrodes and by Bradley and Elkes [7] with atropine and physostigmine in cats. Bradley, Cerquiglini, and Elkes [8] found that in cats isofluorophate duplicates the effects of physostigmine and that isofluorophate also replaces the alternating cortical sleep-alertness picture of the electrocorticogram of the *encephale isolé*, as well as sleep patterns induced by thiopental (Pentobarbital), by the alert EEG pattern.

Another anticholinesterase substance, tetraethylpyrophosphate (TEPP), used by Pscheidt and Stone [9] in dogs, was also found to evoke the alert EEG pattern. Beside these experimental findings, it has been reported that a common clinical symptom following the administration of isofluorophate † and of TEPP [12] in human subjects is sleeplessness and that atropine counteracts this, as well as the other isofluorophate- and TEPP-induced effects.

These data are consistent in indicating that, in general, cholinergic substances favor a shifting of the EEG activity toward alertness. Atropine, however, has the opposite effect, not only when employed as an antagonist to cholinergic drugs but also when used by itself. In regard to atropine, it is important to note the dissociation between the alert behavior of the animal and the absence of an alert EEG pattern, an observation made by

From the Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital.

Read before the Eighth Annual Meeting of the American Electroencephalographic Society, June 11, 1954, at Atlantic City, N. J.

Fulbright Fellow, on leave from the Clinic for the Diseases of the Nervous System of the University of Cagliari, Cagliari, Italy (Dr. Rinaldi).

* References 2 and 3.

† References 10 and 11.

Funderbunk and Case [5] and Bradley and Elkes,[7] as well as by Wikler,[6] who placed strong emphasis on the dissociation.

In the present paper we report the results of studies on the effects of intracarotid ACh, of isofluorophate, and of atropine on the electrical brain activity of the rabbit, with special consideration for the phenomenon called the arousal reaction, or the alerting, or the activating response.

METHODS

Adult albino rabbits, ranging in weight from 2.3 to 3.2 kg., were used. All experiments were performed under artificial respiration and curarization. Preliminary control experiments on nonanesthetized, noncurarized rabbits with permanent dural electrodes revealed that curarization, if maintained at a constant adequate level, does not interfere with the spontaneous electrical activity of the brain or with the action of ACh. A common carotid artery was exposed and a T metal cannula inserted, thus permitting the free passage of blood to the head and yet allowing the intracarotid injection of substances through a polyethylene tube connected to the free end of the cannula. The system was washed at frequent intervals with heparin (10 mg. per 100 cc.) in Ringer solution to prevent coagulation. With this method it was possible to inject any substance (ACh for example) without touching the animal. This was of utmost importance because of the nature of the phenomena to be investigated. We were not satisfied until a standard technique of intracarotid injection was perfected, with such precautions that injections of 1 ml. of saline could be given without inducing any sign of EEG arousal. The main precautions taken in order to avoid stimulating the animal were the elimination of noise, of touch, and of pulling and stretching the artery. The intracarotid injections were made in a small volume of fluid and at an even, slow flow, so that the intra-arterial pressure was not raised.

For recording the electrical activity of the brain, openings were made in the skull of a proper size to hold firmly coaxial electrodes. The surface of the outer electrode was in contact with the dura. Four such electrodes were placed, and the external electrodes recorded from the motor and limbic areas of both sides of the cortex. These electrodes had a hole in the center holding a silver needle insulated except at the tip, for recording from subcortical structures: the head of the caudate nucleus, situated below the motor area, and the medial thalamus, underlying the limbic area. The coaxial electrodes were located on the skull 2 mm. anterior to the transverse suture and 2 mm. lateral to the longitudinal suture, for the motor area; and 4 mm. posterior to the transverse suture and 2.5 mm. lateral to the longitudinal suture, for the limbic area. The depth of the subcortical electrodes corresponding to the aforementioned skull sites was 9 mm. from the external skull surface, for the caudate nucleus, and 12 mm., for the thalamus.

Another bipolar coaxial stimulating electrode of stainless steel was introduced through an opening in the skull near the midline, 12 mm. posterior to the transverse suture at a depth of 13 to 14 mm. from the external skull surface, so that its tip was located in the midbrain reticular substance at the level of the anterior quadrigeminal body. The distance between the two bare ends of the coaxial electrode was 2 mm. In each brain used the intracerebral tract and the site corresponding to the tip of each subcortical electrode were checked by means of serial sections of formalin-fixed, paraffin-embedded whole brain. The sections were stained with the Klüver and Barrera [13] combined technique for myelin sheaths and nerve cells.

Brain electrical activity was recorded with an eight-channel, ink-writing electroencephalographic instrument (Grass D #3). In most of the experiments the ECG was recorded. Blood pressure variations were also observed by means of a cannula inserted in a femoral artery and connected to a mercury manometer. To stimulate the midbrain reticular substance, a Grass stimulator (Model S-4) was used in connection with an isolation unit. Having determined that in the rabbit maximal alerting electric responses were best obtained with stimuli of frequency ranging around 250 c/s (the same is true for the cat, Moruzzi and Magoun [14]), we employed direct-current pulses of a frequency of 250 c/s and a duration of 2 msec., varying the length of stimulation (0.5 to 3 seconds) and the voltage (1 to 8 volts) applied. These procedures were followed routinely in the majority of the experiments (53 animals).

The drugs employed in this study were as follows: acetylcholine chloride (Merck), in freshly made solutions containing 0.5, 1, 2, 10, or 20γ per milliliter; isofluorophate, in freshly made 0.1% solution; atropine sulfate in 1% solution, and chondodendron tomentosum extract, purified (Intocostrin).

RESULTS

I. *Electrical Activity of Unanesthetized, Curarized Rabbit.* — Under these experimental conditions the electrical activity of different parts of the brain shows more or less rapid alternating changes in the general EEG picture, the extremes being the "sleeping" and the "alert" pattern. There are also intermediate pictures representing different degrees of alertness, or, better, different stages of sleep. For purposes of description,

we shall make a distinction only between sleep and alertness, including in the term sleep conditions which could be better termed drowsiness.

A. Characteristics of Sleeping Patterns (Fig. 1): In the anterior part of the rabbit cortex with a center on the motor area, a slow basic activity is observed (1 to 3 c/s), high in voltage (150μv to 300μv) and more or less regular. This pattern frequently occurs in regular runs of 3 or 4 slow waves, but is interrupted at intervals by 12 to 14 c/s spindle-like trains of waves (50μv to 20μv). The spindles may appear in bursts or may ride large slow waves. Besides these two main components, other activities may be more or less evident in ranges of frequencies of 3 to 4 and 5 to 6 c/s, usually as modulations of the basic slower frequency.

The activity recorded from the caudate nucleus follows in general the pattern of the motor area but with reduced amplitude, sometimes with asynchronicity and also with phase reversals. The 4 c/s spindles are almost as constant in the caudate as in the motor cortex but smaller, often, especially in deep sleep, resembling monophasic points (positive to the surface).

The limbic cortex shows an activity which, compared with that of the motor cortex, has less regular 1 to 2 c/s components, more 3 to 4 and 5 to 6 c/s components, and spindles of 14 c/s, clearly of smaller amplitude. The last are absent in many animals. In the thalamus the frequencies of 2 to 3 c/s and 5 to 6 c/s are intermingled; slower activity (1 to 2 c/s) is not as prominent as in the motor cortex, and in the great majority of animals the 14 c/s spindles are absent.

B. Characteristics of Alert Patterns (Fig. 1): An EEG arousal is characterized by an abrupt and simultaneous change in the activity of all brain structures. An instantaneous disappearance of all slow activities and of the 14 c/s spindles results in a flattening of the record. A fast, 22 to 30 c/s activity is dominant in the motor cortex and in the caudate nucleus. In the thalamus a 6 c/s rhythm, extremely regular both in amplitude and in continuity, of medium voltage (50 to 100μv), replaces all other activities. This characteristic thalamic rhythm may occur with reversed polarity in the limbic cortex and in the motor cortex, and oftener in the former than in the latter; least of all is it seen in the caudate nucleus, where the fast frequencies dominate.

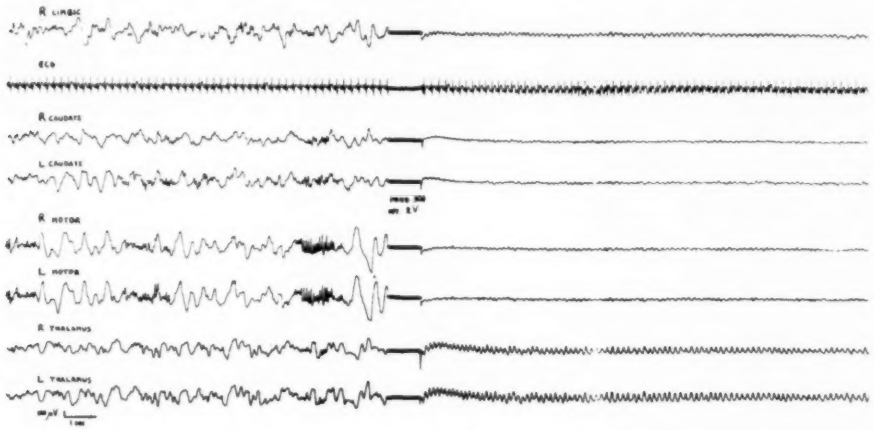


Fig. 1.—Patterns of electrical activity of various parts of the rabbit's brain: alert pattern in the right half of the figure; sleep pattern in the left half of the figure. The alert pattern has been elicited by electrical stimulation of the midbrain reticular formation (square impulses at a frequency of 30 c/s; intensity 2 volts for a duration of 1 second).

Leads (from above downward): (1) right limbic cortex; (2) ECG; (3) right caudate nucleus; (4) left caudate nucleus; (5) right motor cortex; (6) left motor cortex; (7) right thalamus; (8) left thalamus.

We shall omit discussion concerning the details of the electrical activity of the rabbit's brain for a later publication, which will include comparison with the observations of other investigators (Kornmüller,‡ Ectors,[18] Gozzano,[19] Fields and associates,[20] Winokur and associates,[21] and Bovet and Longo [22]). But it is not out of place to emphasize here that in the present investigations the alerting response is not characterized only by the suppression of the sleep patterns (i. e., slow activity and spindles). In addition to the desynchronization of cortical activity and to the development of fast activity, there is the concomitant appearance of a steady, remarkably regular rhythm of thalamic origin. As far as the diffuse thalamic projection system (Jasper,[23] Morison and Dempsey §) and its activation through the midbrain reticular formation (Starzl and Magoun [26]) are concerned, the relationship between the thalamic 5 to 6 c/s rhythm and the part played by the thalamus in the regulation of the electrical cortical activity is highly suggestive.

C. Alerting Reactions Produced by Different Methods: The characteristics of the EEG changes are the same no matter what type of stimulus is used. The chief difference lies in the duration of the alert pattern following arousal. For example, in the same animal under the same conditions, the duration of an alert reaction is shorter after an auditory or a tactile stimulus than it is after a pain stimulus. The maximal duration is observed after electrical stimulation of the midbrain reticular substance.

D. Influence of Level of Curarization: If the curarization is not complete, periods of alertness tend to occupy the major part of the record, and all types of stimuli seem to be more effective, especially in regard to the duration of the response. If the level of curarization is so low that some muscle fasciculation is possible, even without efficient contraction, then the EEG record shows predominantly the alert characteristics. Obviously, a continuous flow of proprioceptive stimulations is set up to favor and maintain an alert status.

E. Ventilation and Blood Pressure: If the rate or the volume of artificial respiration is excessive, the sleep pattern is favored, the slow waves increase in voltage, and the 14 c/s spindles become more numerous. But the onset of an arousal reaction is not prevented, even if the stimulus is very light: Only the duration of the alert pattern tends to be shorter. If ventilation is insufficient, the reverse situation occurs, and sleep patterns are of shorter duration. In an animal with an unstable blood pressure, showing a tendency to low blood pressure and frequent oscillations around low values, the electrical pattern is likely to be continuously activated, with only transitory sleep periods. A rapid fall in blood pressure produces abnormal waves, very slow (1 or 2 c/s), not of the type seen in sleep, but resembling those produced by asphyxia, especially if the original blood pressure level is low. A steady blood pressure (at systolic levels between 70 and 120 or with slow variations between those limits) is optimal for maintenance of a normal EEG.

II. *Action of Intracarotid Acetylcholine* (Fig. 2).—The injection of a small dose of ACh in the common carotid artery induces an instantaneous alerting reaction. The modification of the electrical activity of the brain is identical to that produced by any stimulus, such as sound, touch, or pain, or by a direct electrical stimulation of the midbrain reticular substance. The effect of ACh is immediate and occurs simultaneously and symmetrically in all parts of the brain, in spite of the fact that the injection is made through the artery of one side.

ACh first becomes effective with a dose of 0.5γ. With larger doses, of 1γ to 5γ, the action is best developed and of longer duration. Further increase of the dose reveals not only the alerting effect, but also systemic pharmacological activity on the heart and blood pressure. After a short delay there is a slowing of the heart rate that follows the onset of the alerting changes in the EEG. At doses between 15γ and 25γ the action on the heart

‡ References 15, 16, and 17.

§ References 24 and 25.

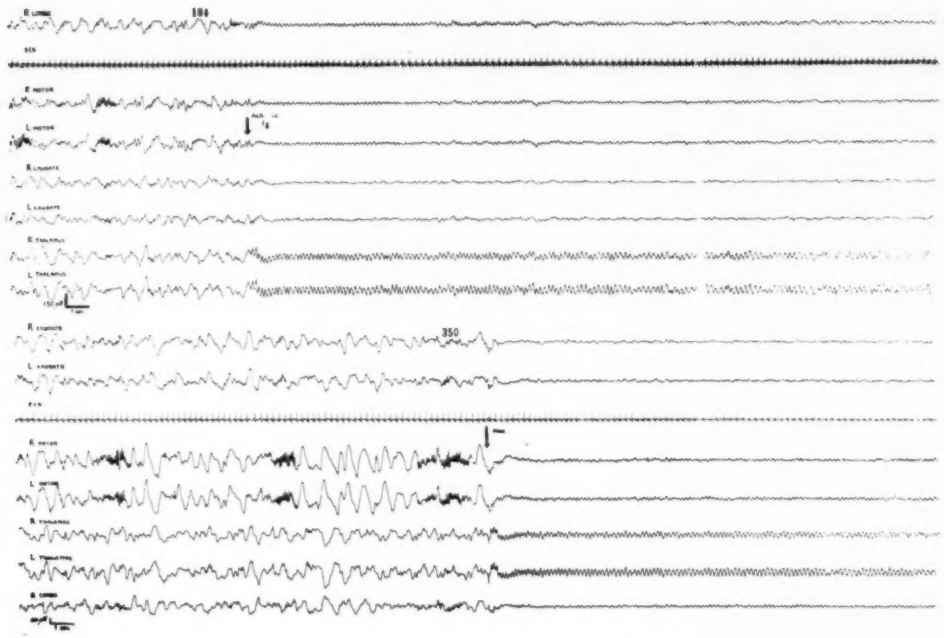


Fig. 2.—Upper record: an alerting reaction induced by the injection (at the arrow) of 1γ of acetylcholine into the right common carotid artery.

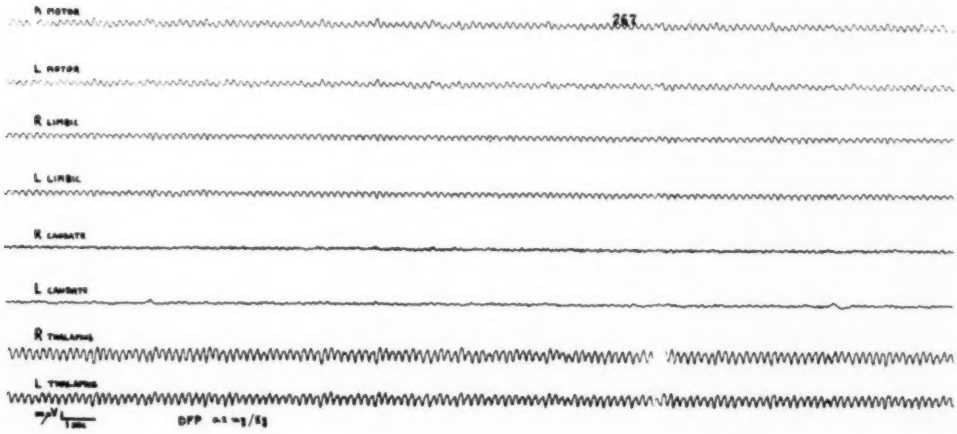
Leads (from above downward): (1) right limbic cortex; (2) ECG; (3) right motor cortex; (4) left motor cortex; (5) right caudate nucleus; (6) left caudate nucleus; (7) right thalamus; (8) left thalamus.

Lower record: an alerting reaction induced by pain stimulation (at the arrow).

Leads (from above downward: (1) right caudate nucleus; (2) left caudate nucleus; (3) ECG; (4) right motor cortex; (5) left motor cortex; (6) right thalamus; (7) left thalamus; (8) right limbic cortex.

Fig. 3.—Long-lasting alert EEG pattern produced by the injection of isofluorophate (0.2mg/kg.) into the right common carotid artery.

Leads (from above downward): (1) right motor cortex; (2) left motor cortex; (3) right limbic cortex; (4) left limbic cortex; (5) right caudate nucleus; (6) left caudate nucleus; (7) right thalamus; (8) left thalamus.



and blood circulation becomes so intense that a rapid fall of blood pressure ensues, and the electrical activity of the brain takes on the characteristics of asphyxia, with extremely slow waves and flattening of the record.

III. *Action of Isofluorophate* (Fig. 3).— Isofluorophate was administered in doses not sufficient to induce convulsive activity (Freedman and associates [27]). A progressive change in the electrical activity of the brain takes place after intracarotid injection of the drug in divided doses of 0.05 mg/kg. until a total dosage of 0.1 to 0.3 mg/kg. is reached. The slow waves and 14 c/s spindles gradually decrease in number and amplitude until they disappear completely. In the thalamus a 6 c/s rhythm becomes more and more apparent and regular until it overcomes all other activity, and finally the whole record shows the full EEG picture of alertness. In addition, a second action of isofluorophate can be distinguished. The general accumulation of ACh, due to the anticholinesterase activity of isofluorophate, tends to overcome the effect of curare. Muscle twitching appears early, a sign of a nicotinic effect of isofluorophate, together with salivation, bradycardia, miosis, and the other muscarinic actions.

But if more curare is given, the nicotinic effect on the muscles is neutralized and the twitching disappears. The effect of the additional dose of curare on the electrical activity of the brain is that sleep patterns are restored if the dose of isofluorophate is small (0.05 to 0.1 mg/kg.). But if the amount of isofluorophate is large (0.2 mg/kg.), or if after curare more isofluorophate is given, the sleep patterns fail to reappear in spite of the fact that muscle twitching is completely abolished. The alert pattern induced by isofluorophate continues unbroken for hours, with its 4 to 6 c/s thalamic rhythm more or less spreading to other parts of the brain and with fast activity in the motor area and caudate nucleus. Further administration of curare does not affect the isofluorophate-induced pattern.

The use of the intravenous route instead of the intracarotid one for isofluorophate makes no difference in regard to the above-mentioned effect; only a slightly larger dose is required.

IV. *Action of Atropine on Acetylcholine- and Isofluorophate-Induced Effects.*— The administration of atropine sulfate i. v. is definitely antagonistic to the alerting action of intracarotid ACh. This antagonism becomes apparent with 0.5 to 1 mg/kg. of atropine as a marked shortening of the duration of the alert EEG pattern following ACh administration. The effect increases with larger doses until, with about 2 mg/kg. the action of ACh is entirely prevented. Even 10γ to 20γ of ACh given by intracarotid administration fails to modify the electrical activity of the brain.

When atropine is given to an animal under the influence of isofluorophate, the automatic alert pattern of the electrical brain activity is readily broken; the thalamic 4 to 6 c/s is disrupted by incoming slower frequencies; in the other regions the typical slow high-voltage waves appear, together with the 14 c/s spindles, the latter prominent in the motor area.

This action of atropine is progressive, is related to the dose of isofluorophate the animal has received, and is ordinarily fully established with 3 to 4 mg/kg. of atropine. The higher the amount of isofluorophate, the larger the dose of atropine required. If the amount of atropine is insufficient, its action on the electrical pattern is incomplete; the alert pattern is disrupted by slow waves and also by spindles for short, discontinuous periods.

When the action of isofluorophate has completely disappeared, owing to the administration of atropine, additional injections of isofluorophate counteract the effect of atropine and restore the alert pattern. By alternating atropine and isofluorophate, the phenomenon can be reproduced repeatedly. We have been able to reverse the EEG picture as many as four times in the same animal, finally attaining total doses of 1.5 mg/kg. of isofluorophate and 30 mg/kg. of atropine with no effect on the EEG activity other than the alternation of the alert and sleeping patterns.

V. *Universal Inhibitory Action of Atropine on Alerting Reactions* (Fig. 4).—Besides these effects antagonistic to the ACh- and isofluorophate-induced alert pattern, atropine has by itself a general action on the electrical brain activity. As suggested by the results of Funderburk and Case,[5] Wikler,[6] and Bradley and Elkes,[7] we have observed that atropine exaggerates the EEG sleep patterns; the general voltage is increased because of the larger amplitude of the slow waves and of the spindle activity. Moreover, atropine inhibits the alerting EEG response to all sorts of stimuli.

Beginning at doses of 1 to 2 mg/kg., it can be noted that the generalized activation caused by sound disappears and that the duration of the activation following tactile and pain stimuli or electrical stimulation of the midbrain is greatly reduced. However, the other characteristics of the alert pattern are unchanged. With larger doses of atropine, beginning with 3 mg/kg., the blocking effect for all types of alerting responses increases progressively. In general, with 3 to 6 mg/kg. no reaction follows a strong pain stimulus. The threshold of the midbrain reticular substance to electrical stimulation is also greatly increased, and the reaction that follows is not enduring but barely outlasts the stimulation period.

With doses of 10 mg/kg. or more the blocking effect of atropine is total; yet the general picture of the EEG is not different from that following a dose of 3 mg/kg. of atropine. Even doses as large as 30 mg/kg. do not have different effects. It is interesting to note that even in an animal under the action of a blocking dose of atropine, an adequate amount of isofluorophate still restores the normal responsiveness of the EEG to alerting stimuli. In contrast to the isofluorophate-induced convulsions, which can be prevented or checked by atropine,[27] the electrical production of convulsions is not depressed by atropine.

Therefore atropine and isofluorophate exert exactly opposite actions on the EEG. Atropine inhibits the alerting responses, while isofluorophate facilitates them; atropine crystallizes the pattern of the electrical activity of the brain in a sleep-resembling picture, while isofluorophate induces a steady pattern of alertness.

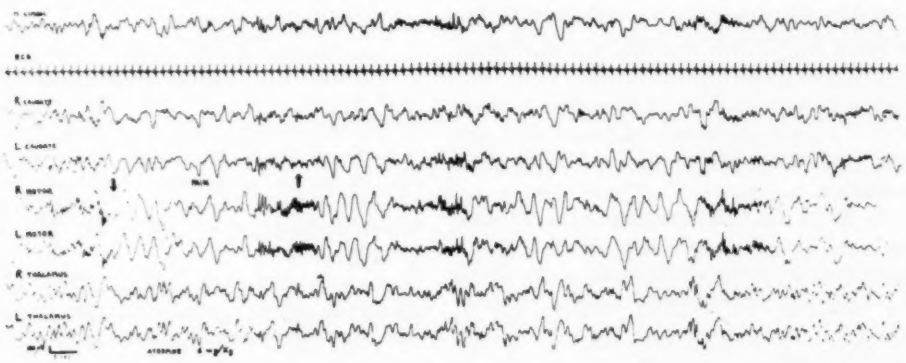


Fig. 4.—Complete absence of alerting reaction to pain stimulation (between arrows) as a consequence of the administration of atropine (6 mg/kg. i.v.).
Leads as in Figure 1.

We have seen that no narcotic effects are produced by blocking doses of atropine in noncurarized, unrestrained rabbits, as Wikler [6] has previously demonstrated for the dog. The animals are behaviorally alert; yet the electrical activity of their brains is one of continuous sleep.

COMMENT

Our data show that ACh and isofluorophate produce a diffuse abrupt change of the brain electrical activity identical with an alerting reaction. The effect of ACh is transi-

tory, while that of isofluorophate is long-lasting. Since we know that isofluorophate inhibits brain cholinesterase and permits the accumulation of ACh (Michaelis and associates [28]), it is reasonable to assume that the identical changes produced by ACh and isofluorophate are due to the same mechanism: a cholinergic one. The fact that atropine prevents and neutralizes the changes produced by ACh and isofluorophate confirms the conclusion that a cholinergic action of the type that is inhibited by atropine is involved.

We have seen that atropine not only acts as an inhibitor of the central effects of cholinergic drugs but also suppresses the alerting effects of sensory excitation and of the direct electrical stimulation of the midbrain reticular substance. In the rabbit that has received high doses of atropine, the electrocorticogram shows a stable pattern of sleep that cannot be modified by stimulation of any sort. It is impossible to produce an alert pattern and thus desynchronize the sleeping potentials.

So far as the EEG changes are concerned, the central action of atropine can be described as a selective inhibition of the alerting reaction. The alerting reaction is produced by the setting into activity of the mesodiencephalic activating system (midbrain reticular formation of Moruzzi and Magoun [14] and thalamic diffuse projection system of Jasper [23]).

Our results are consistent in indicating that the function of the activating system in the atropinized animal is paralyzed, while it is overactive in the animal that has received a cholinergic drug. These considerations strongly suggest the hypothesis that the function of the mesodiencephalic activating system be cholinergic in nature. Such a hypothesis explains fully the changes induced by cholinergic drugs and by atropine on the electrical activity of the brain, implying that the mesodiencephalic activating system is the principal site of action of those drugs.

SUMMARY AND CONCLUSIONS

Acetylcholine produces a diffuse abrupt and transitory change of the brain electrical activity identical with an alerting reaction.

Isofluorophate produces a long-lasting steady EEG pattern of alertness.

Atropine prevents and neutralizes the effects of ACh and isofluorophate.

Atropine by itself evokes an EEG pattern of sleep and inhibits all alerting reactions produced by physiological stimuli and by direct stimulation of the midbrain reticular substance.

It is suggested that the mesodiencephalic activating system is the specific site of action of atropine and cholinergic drugs.

The hypothesis that a cholinergic mechanism is involved in the function of the mesodiencephalic activating system best explains the present observations.

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Cholinergic Mechanism Involved in Function of Mesodiencephalic Activating System

FRANCO RINALDI, M.D.
and
HAROLD E. HIMWICH, M.D., Galesburg, Ill.

A previous investigation [1] dealt with the action of cholinergic drugs and of atropine on the electrical activity of the rabbit brain. It was found that acetylcholine (ACh) produces a transitory change of the brain electrical activity identical with the alerting reaction evoked by a peripheral stimulus or direct stimulation of the midbrain reticular substance.[2] Isofluorophate (diisopropyl fluorophosphate; DFP), a powerful anticholinesterase agent, induces a long-lasting and continuous electroencephalographic pattern of alertness. On the other hand, atropine prevents all electroencephalographic alerting reactions, no matter how elicited. The pattern of alertness is due to the setting into activity of those mesodiencephalic structures with diffuse projections over the entire cortex, such as the midbrain reticular substance of Moruzzi and Magoun [2] and the thalamic diffuse projection system of Jasper.[3] It seems that cholinergic drugs exert a primary excitation on the mesodiencephalic system, while atropine enforces a primary paralysis of the same system. We suggested in our previous publication [1] that the site of action of cholinergic and anticholinergic drugs is located at the mesodiencephalic level. We also formulated the hypothesis that a cholinergic mechanism is involved in the function of the activating system because of the opposite effects of cholinergic and anticholinergic drugs upon it. Against these hypotheses objections could be raised in the form of alternative explanations. First of all, the effect of the drugs in question might be secondary to their parasympathetic action on cerebral blood vessels. In fact, Darrow's * hypothesis of a parasympathetic regulation of the electrical activity of the brain suggests that the desynchronization of the brain waves produced by cholinergic drugs is secondary to the dilatation of cerebral blood vessels. Beside the effect on these vessels, there is the possibility that cholinergic drugs stimulate peripheral receptors directly,† so that a flow of afferent impulses could reach the brain from the periphery and produce the alerting effect. Still another possibility is the indirect feedback of afferent impulses from smooth muscles, glands, blood vessels, and striated muscles, a secondary result of the muscarinic or nicotinic action of cholinergic drugs.

To test our hypothesis that the mechanism of action of the parasympathomimetic and parasympatholytic drugs is central, it seemed necessary to investigate whether or not the drugs were still effective after the interruption of all afferent pathways. It was also important to determine the relationship of changes in brain circulation to the phenomenon of electroencephalographic alerting.

From the Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital.

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Fulbright Fellow on leave from the Clinic for the Diseases of the Nervous System of the University of Cagliari, Cagliari, Italy (Dr. Rinaldi).

* References 4 through 7.

† References 8 and 9.

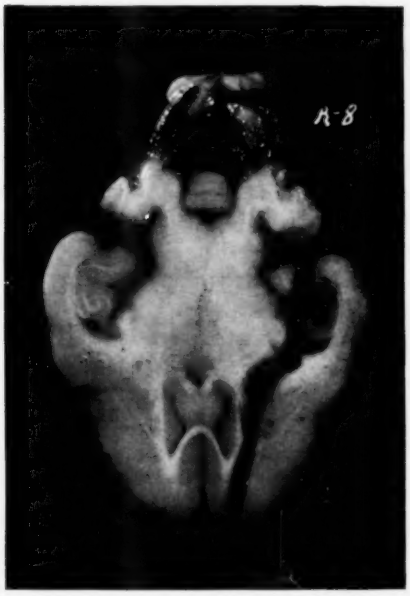

Fig. 1.—Preparation with "isolated" left hemisphere. Horizontal section at level of corona radiata. The picture shows the location and extent of the cut that completely severs the connections of the left hemisphere with the rest of the brain.

Even if a direct effect on the brain could be demonstrated, it still remained to be decided whether the activation of the EEG is merely a sign of a diffuse, undifferentiated effect on all cerebral structures or the result of stimulation of a specific system, such as the midbrain activating system of Moruzzi and Magoun [2] and the thalamic diffuse projection system of Jasper.[3] It was with these questions in mind that the present study was undertaken.

METHODS

All experiments were performed on adult albino rabbits, curarized and maintained by artificial respiration. For recording the electrical activity of the brain, electrodes were placed on the motor cortex, in the head of the caudate nucleus, on the limbic cortex, and in the medial thalamus, with a technique identical to that previously described.[1] Another electrode (bipolar, of stainless steel) was placed so that its tip was located in the midbrain reticular substance at the level of the anterior quadrigeminal body. This electrode was used for direct stimulation of that formation. In all brains used the intracerebral location of the electrodes was checked by means of serial sections of formalin-fixed, paraffin-embedded whole brain. The sections were stained with a combined technique for myelin sheaths and nerve cells.[10] Brain electrical activity was recorded with an eight-channel ink-writing electroencephalogram (Grass Model D). To stimulate the midbrain reticular substance, direct-current pulses of a frequency of 300 a second and a duration of 2 msec. were employed. The voltage of stimulation (1 to 8 volts) and the duration of application of the stimulus (0.5 to 3 seconds) were so adjusted that stimuli were always slightly above threshold values. These parameters had been found optimal for the production of the alerting reaction in our preceding study.

Administration of ACh was made through an intracarotid cannula. Atropine was administered intravenously, while isofluorophate was injected both intravenously and into the carotid artery. For other technical details see Rinaldi and Himwich.[1]

In one group of animals surgical separation of one hemisphere from the rest of the brain was made in such a manner as to leave its blood supply intact. The operative procedure included a longitudinal monolateral craniotomy along the midline, through which the dura was opened. The connections of one cerebral hemisphere with the rest of the brain were severed by using a blunt spatula to cut through the corpus callosum, anterior commissure, fornix, and capsula interna. The cut ran external to the thalamus, but through the medial part of the corpus striatum, which was therefore somewhat damaged (Fig. 1). Vascular connections were preserved.

Fig. 2.—*Cerveau isolé* preparation, a midline longitudinal section. The picture shows the complete transection at the level of the posterior quadrigeminal body.

In this report we are including only the results obtained from isolated hemisphere preparations (five animals) that on examination proved to be completely separated and free of complications, such as hemorrhages.

In another group of animals a midbrain section was performed with a transverse cut from the posterior colliculus to the ventral surface of the rostral end of the pons, thus obtaining a *cerveau isolé* preparation (Fig. 2).

RESULTS

"Isolated Hemisphere" Preparations.—In the "isolated hemisphere" preparation the entire cerebral cortex of one side, together with the parts of the basal ganglia outside the cut, as previously described, is deprived of all connections with the rest of the brain. Only the blood supply is preserved. The electrical activity recorded from the cortex of the isolated hemisphere of acute preparations, one to three hours old, can be described as dominated by random slow activity of low and medium amplitude, completely independent of, and unrelated to, the activity of the rest of the brain, which remains entirely normal (Fig. 3). If in this preparation with isolated hemisphere an alerting reaction is induced in various ways (electrical stimulation of the midbrain activating system, or by intracarotid injection of ACh, or by a dose of isofluorophate adequate to produce an enduring alerting EEG pattern), the effects involve the thalamus and the structures of the intact hemisphere in the usual manner. The activity of the isolated hemisphere, however, with its independent random slow patterns, continues unmodified (Fig. 4: upper tracing). If a change occurs in the activity of the isolated hemisphere during the action of isofluorophate, it is an increase in amplitude of the slow random waves, but never a desynchronization or the appearance of a

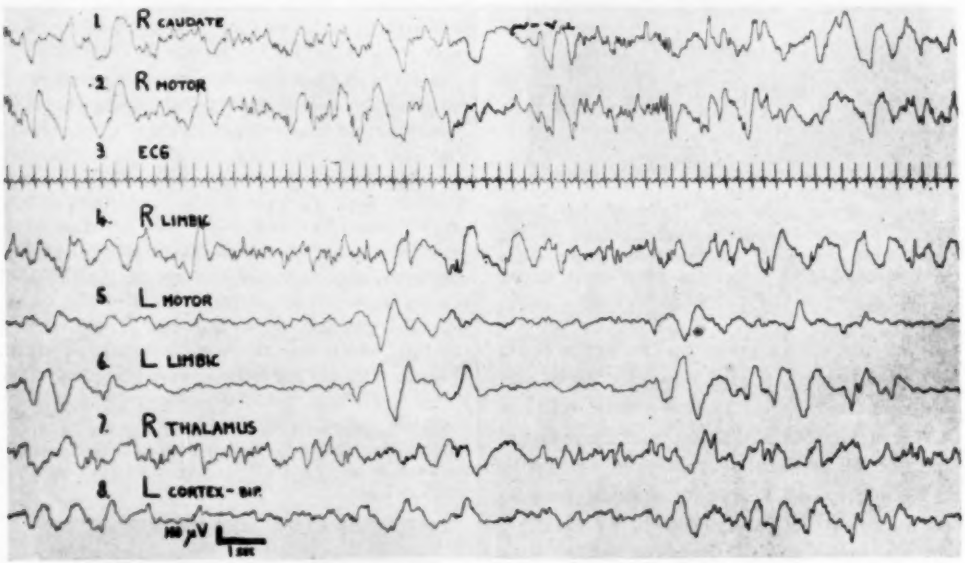

Fig. 3.—Isolated hemisphere preparation. The connections of the left hemisphere with the rest of the brain were severed 30 minutes before this record was taken.

Leads (from above downward): (1) right caudate nucleus; (2) right motor cortex; (3) ECG; (4) right limbic cortex; (5) left motor cortex; (6) left limbic cortex; (7) right thalamus; (8) left motor-left limbic cortex.

The animal was kept undisturbed, and the electrical activity of the intact parts of the brain shows the sleep pattern (see also Figure 1, Rinaldi and Himwich [1]): high-voltage (150 to 300 volts), slow (1 to 3 c/s) waves and spindles of 12 to 14 c/s waves in the motor cortex, in the caudate nucleus, and in the limbic cortex (the spindles are more prominent in the motor cortex); 1 to 3 c/s activity intermixed with 5 to 6 c/s frequencies in the thalamus. In the cortex of isolated hemisphere (leads 5, 6, and 8) only independent random slow activity is present.

4 to 6 c/s rhythm, characteristic of an alerting response.

The administration of atropine in the isolated hemisphere preparation does not modify the electrical activity of the cortex disconnected from the rest of the brain (Fig. 4: lower tracing). All other parts of the brain show the same modification in their electrical activity to the administration of atropine as rabbit the work of Bradley and co-workers [11] in the cat. In the *cerveau isolé* animals all connection between the midbrain and the lower nervous system are sectioned. In the immediate postoperative stage the electrical activity of the *cerveau isolé* preparation is characterized by a flattening of the electrocorticogram because of the dominance of fast frequencies of very low voltage, while in

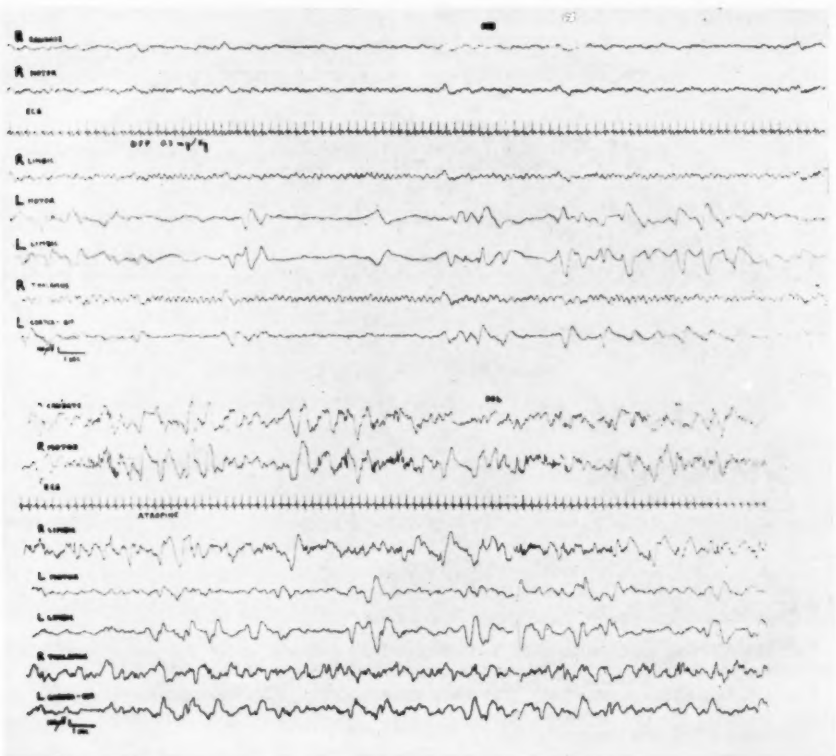

Fig. 4.—Same animal as in Figure 3; leads as in Figure 3.

Upper tracing: After 0.3 mg/kg. of isofluorophate, i. v. The pattern of alertness is continuous and dominant in the intact parts of the brain. Fast activity at low voltage in right caudate nucleus and in right motor cortex. In the thalamus and in the right limbic cortex, see the typical 4 to 6 c/s rhythm of thalamic origin. (Compare with Figure 1, Rinaldi and Himwich [1]). In the cortex of the isolated left hemisphere the random activity continues unmodified, despite the administration of isofluorophate.

Lower tracing: After atropine, 4 mg/kg., i. v. In the intact parts of the brain the alert pattern has disappeared, and the characteristics of sleep are restored (compare with Figure 3). In the isolated left hemisphere the random slow activity continues.

they do in the intact animal. The isolated hemisphere, however, continues to exhibit its random slow activity.

Cerveau isolé *Preparations.*—With the *cerveau isolé* experiments we repeated in the the electrothalamogram a 5 to 6 c/s rhythm is outstanding.

Within 15 to 30 minutes the EEG gradually returns to a pattern similar to the one of normal sleep, with high-voltage slow waves

and 14 c/s spindles. Intermittently, short periods of activity of the alert type interrupt the sleeping pattern.

In this *cerveau isolé* preparation any type of peripheral stimulation, such as sound, touch or pain, is unable to produce an alerting reaction. In contrast, the direct stimulation of the upper midbrain reticular formation (electrode in the medial tegmentum at the level of the anterior quadrageminal body) above the section evokes the alerting reaction. Similarly, the intracarotid injection of ACh (0.5γ to 15γ) still causes an alerting response (Fig. 5). The administration of isofluorophate (0.2 to 0.3 mg/kg.) induces a long-lasting, continuous, and regular alert pattern.

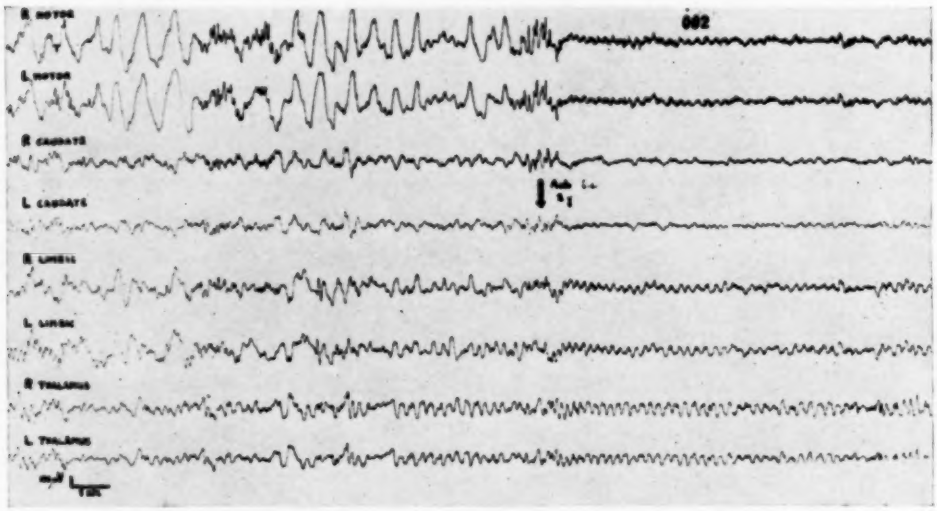

Fig. 5.—Alerting reaction induced in a *cerveau isolé* preparation by injection of acetylcholine (2γ) into right common carotid artery (at arrow).

Leads (from above downward): (1) right motor cortex; (2) left motor cortex; (3) right caudate nucleus; (4) left caudate nucleus; (5) right limbic cortex; (6) left limbic cortex; (7) right thalamus; (8) left thalamus.

Atropine (2 to 10 mg/kg.) counteracts and prevents the action of ACh and isofluorophate, and even inhibits the alerting response to direct electrical stimulation of the midbrain tegmentum.

COMMENT

In the *cerveau isolé* preparations all afferent pathways are interrupted at the caudal end of the midbrain. No afferent impulse can reach the midbrain and forebrain (with the exception of the visual and olfactory impulses). Yet intracarotid ACh still produces an arousal reaction. Even if ACh were to stimulate peripheral receptors—for instance, receptors in the arterial wall—there is no known pathway left intact through which the impulses so generated could reach the brain above the mesencephalic transection. Therefore we may say that the alerting reaction produced by intracarotid ACh does not depend on the stimulation of peripheral receptors, or in general on any afferent impulse.

Isofluorophate induces in the *cerveau isolé* preparation the same continuous and long-lasting pattern of EEG alertness as in the intact animal. Again, in the case of isofluorophate, a stimulation of peripheral receptors, as described by Brown and Gray [8] for ACh and nicotine, cannot be held responsible for evoking the EEG pattern of alertness. Moreover, atropine maintains in the *cerveau isolé* animal its property of blocking arousal reactions and of preventing and counteracting the alerting effect of cholinergic drugs. The mechanism for this action of atropine cannot be sought in a peripheral source.

In the isolated hemisphere preparation, the cerebral cortex of one side is deprived of all its neuronal connections with the rest of the brain, though maintaining its vascular connections. The random slow electrical activity of the cortex of the isolated hemisphere does not change, while the alerting reaction induced by intracarotid ACh spreads over the rest of the brain. Similarly, isofluorophate calls forth a continuous alert pattern in all parts of the brain, with the exception of the isolated hemisphere. ACh was injected into the carotid artery of the side of the isolated hemisphere, and isofluorophate was injected both into the carotid artery and intravenously, with no difference in results. Since the blood supply to this isolated hemisphere is left intact, the drugs must reach this isolated hemisphere as well as (or, in the case of homolateral intracarotid injection, better than) the rest of the brain. If a general diffuse action of the cholinergic drugs were responsible for the alert EEG pattern, the electrical activity of the isolated hemisphere should show signs of electrical awakening. But such activation fails to appear. Therefore the cholinergic drug must produce electroencephalographic alerting through an action not on the cerebral cortex but on the mesodiencephalic neuronal mechanism with diffuse projection over the cortex.

The electrical alerting of the cortex depends on the integrity of its neuronal connections with mesodiencephalic structures. This relationship holds for the cholinergic-drug-induced alerting, as well as for that evoked by any other means. In our preparation the electrical stimulation of the midbrain reticular formation produces desynchronization of the activity of all parts of the brain with the exception of the isolated hemispheres. This fact is an addition to the body of evidence indicating that the electrical arousal is mediated through the mesodiencephalic activating system.‡

The observations made in the isolated hemisphere preparation show that the atropine-induced changes of the EEG pattern also fail to appear at the level of the isolated cortex. Therefore, the action of atropine is also primarily exerted on the mesodiencephalic activating system. Atropine is a specific depressant for the function of that system.

The same facts that exclude the hypothesis of a diffuse action of cholinergic drugs and of atropine also eliminate the supposition that the EEG changes are secondary to vasomotor effects in the brain area. According to the theory of the parasympathetic regulation of the EEG,§ the disappearance of the slow-frequency, high-voltage waves, with the substitution of fast, low-voltage activity, is secondary to the dilatation of brain vessels. But in our experiments the slow activity recorded from the isolated hemisphere was not eliminated by the vasodilatation resulting from the intracarotid injection of ACh. The alerting effect is therefore not secondary to vasodilatation.

All our results are consistent in indicating that the changes of the electrical brain activity following the administration of cholinergic drugs and atropine are mediated through a specific action of those drugs on the mesodiencephalic activating system. In the atropinized animal the function of the activating system is paralyzed, while it is overactive in the animal that has received a cholinergic drug. There is only one explanation consonant with all these results: The function of the mesodiencephalic system is cholinergic in nature.

SUMMARY AND CONCLUSIONS

The electroencephalographic alerting response following the intracarotid injection of ACh and of isofluorophate (DFP) is not prevented by transection at the level of the lower midbrain; this excludes a peripheral mechanism.

Under the influence of cholinergic drugs an electroencephalographic alerting is not detectable in the cortex of an isolated hemisphere having all neuronal connections with the rest of the brain sectioned. The effect is, therefore, not due to a diffuse action of the

‡ References 2, 12, and 13.

§ References 4 through 7.

drug on the cerebral cortex, nor is it secondary to dilatation of brain blood vessels.

The site of action of cholinergic drugs and of atropine in producing diffuse changes of the EEG patterns is at the mesodiencephalic level.

Cholinergic drugs stimulate selectively the function of the mesodiencephalic activating system.

Atropine paralyzes selectively the function of the mesodiencephalic activating system.

The function of the mesodiencephalic system is cholinergic in nature.

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An Outline of the Process of Recovery from Severe Trauma

HARLEY C. SHANDS, M.D., Chapel Hill, N. C.

This discussion is an attempt to draw together into a single formulation many separate parts of an experience gleaned during two years of interviewing patients suffering from severe malignant illness of one sort or another.[1] We were impressed at the time, and have continued with increasing interest to be impressed, with the manner in which, after the imposition of intolerable stresses, the resultant strains point up the basic similarity of human patterns in personality disintegration and in the restitution which follows. Further, we may by analogy make certain inferences about early personality development.

In the field of research into human developmental patterns the direct experimental imposition of stress of a degree sufficient to impose strain upon the resources of the individual is impossible: Either the stress is inadequate to present any major adaptive problem to the individual, or else the conditions of the experiment are apt to exceed the limits of the taboos upon experimenting with human beings. However, the transactions taking place between a patient and his physician in the course of the treatment of a malignant illness present an opportunity for study of reactions of strain which is a reasonable facsimile of an experimental situation. In early cases the informational stress is maximal when the patient discovers the nature of the lesion, and during this period, when the patient remains in good health otherwise, much may be learned of the manner in which informational stresses are managed; on the other hand, with the increasing severity in the lesion and the growing disability of the patient, much may be learned about the somatopsychic problem, i. e., about the manner in which the increasingly morbid process affects the state of mind of the patient and his relation to himself and his environment.

Lest it seem that this program is entirely devoid of any quality of human kindness, it may be noted in passing that one of the most reassuring and gratifying parts of the experience of this period of interviewing was the discovery that the interest displayed in the patients by the interviewer was for the most part welcomed by the patients; many of them spontaneously expressed feelings of gratitude at being able to talk to someone. Indeed, it is entirely probable that in a project such as this, some degree of self-interest on the part of the patient is an indispensable motivational element; particularly in advanced states of disability patients are quite unable to display the altruism involved in giving of information without hope of reward. In accepting the report of the patient's experience the interviewer functions as an important tension-relieving device for the patient. One patient remarked that she had become entirely unable to have any feeling that her family understood anything of the distress through which she was passing, and the surgical staff had no time to listen, so that she was greatly relieved by the attention of the psychiatric interviewer.

The process of restitution, beginning with the imposition of the trauma, may be formulated as a single process which demonstrates from beginning to end an increasing ability on the part of the patient to discriminate in his experience, to differentiate those things

Associate Professor of Psychiatry, University of North Carolina School of Medicine.

which belong together from those which should be separated. In general, it appears that the process is, rather, one in which a whole becomes gradually more and more analyzable into parts than it does one in which new parts are added one by one to construct a whole; by analogy, we may say that it appears to us that a human being characteristically is first aware of the forest and gradually aware of the trees which make it up, with an eventual full awareness both of the individual parts and of the whole.

The formulation which we desire to present in the course of this paper is one which rests upon, and attempts to point out a number of relations among, the work of a number of investigators. The general concept of personality formation and the dynamics of the processes in mentation were formulated in the most influential and striking way by Freud [2]; Goldstein [3] has been concerned with the consequences of brain injury, and especially with certain aspects of the problems of abstraction and concreteness; Melanie Klein [4] has been most instructive in her presentation of the early stages of the organization of the ego, particularly in her formulation of the paranoid position, the depressive position, and the manic defense.

This presentation is necessarily an approximation of a hypothetical solution broad enough to cover the whole process of restitution. It is an effort to describe an abstract, idealized process closely modeled upon the contributions of the investigators we mentioned, and there was no single patient in whom all of the manifestations to be discussed were observed.

The process of recovery can be described in three phases, each of which may be divided into two steps. The first phase is that of the immediate response; the second, that of "total defense," and the third, that of a reintegration of the self. In the first phase, with its steps of chaos and of depersonalization, the patient describes feelings of nonexistence; in the second, the patient defends himself by the exclusion of the unbearable information in stages of projection and of denial, and in the third, in states of depressive anxiety and of novel ego identifications, he describes the loss of his old idea of himself and the construction of a new version which includes the painful information.

A. FIRST PHASE

First Step: Chaos.—In those patients who were suddenly apprised of the nature of their lesion, there was a remarkable stereotypy of immediate response: Almost every patient said the experience was like being struck a heavy blow over the head. Other descriptions included being "stiffened out," paralyzed, made speechless. In all of the patients without other complications, this phase of the response was a very dramatic, but transient, one.

Second Step: Depersonalization.—The immediately succeeding period was characterized as being one of numbness, "going through the motions," feeling as though in a fog. The patients felt remote and alienated from themselves, although able to act in a rote mechanical way. The symptoms are indistinguishable from symptoms of depersonalization encountered elsewhere.

In a case complicated by extensive operation, the two steps could be distinguished, but here the first lasted for several days, during which time the patient lay almost completely inert, responding only to very strong stimuli. When she began again to respond, she described a very marked inhibition in all emotional processes during this period, followed by a feeling of being "all in pieces," of being afraid to look at the region of her wound for fear that she would find "nothing" there.

B. SECOND PHASE

First Step: Projection.—In patients affected by this particular traumatic situation the examples of undiscriminating defense that we have seen have been primarily projection and denial. It appears that such a symptom as amnesia, seen so frequently in other traumatic neuroses, might also be classified under this heading, but we have not observed it in this group. Both these mechanisms appear to be attempts to deal with

the dangerous information by separating it from the self; the attempt is more mature than the preceding one of fragmentation because of the maintenance of a functioning organization which is possible with either projection or denial.

We have been impressed in this series by indications of the more primitive nature of the mechanism of projection, both from the standpoint of the character structure of those patients using this defense rather than another, and by the greater frequency of manifestation of projective mechanisms in the terminal period of the illness.

The defensive use of the mechanism of projection and its sudden collapse on several occasions could be clearly seen in a woman who tended to develop sudden very strong dependent relationships to doctors. When she was relieved by x-rays of a cervical carcinoma, she announced aggressively to everyone what a wonderful man her doctor was because he had cured her cancer; when the cancer recurred, she became very depressed and changed doctors. A second physician promised not to leave her, but after an operation he went to a medical meeting and she became depressed. When seen in an interview for this series, she first reacted with intense gratitude, grasped the therapist's hand, and said no one had listened to her before; but upon the next day's visit, she was very hostile and withdrawn—she said, "Go away, I don't want to see you again; you stirred me all up and made me feel so unhappy yesterday."

While this problem is of immense importance from a theoretical standpoint, it is of equal importance from a practical point of view in the management of patients with cancer, since these patients are on the whole prone to react thus. As a rule, the severer the state of illness, the more likely is the patient to respond by projecting the evil inside onto the external world; but where his world is the hospital, this projecting, leading as it does to a rather paranoid response to the therapeutic personnel, is extremely costly in all ways. Patients report many instances of panic in relation to doctors and nurses; these panic reactions are commoner the sicker the patient, the less sensitive the therapeutic personnel, and, interestingly enough, the more the instance in question takes place in the middle of the night.

A patient in the advanced stages of metastatic illness told us that the nurse was crazy. Another woman reported a very severe panic when awakened in the night by the delirious rambling of a neighboring patient—she wondered what terrible things doctors were doing to her; this woman had severe anxiety when the service changed, since she was afraid of strange doctors; on another occasion she reported that a nurse in giving her a back rub had dug her fingers all the way down to the bone, a feeling which terrified her.

Second Step: Denial.—The second of these undiscriminating defenses, that of denial, is of less importance from a psychotherapeutic standpoint for two reasons: In the first place, it is a defense which does not, as in the case of projection, lead onward in a vicious circle to greater and greater distress—the patient dismisses the problem by denying its existence and the process tends to come to a stop until further events occur; in the second place, for some patients a stabilized position of denial in the face of a hopeless lesion is as good a situation as can readily be attained. Where the defense of denial carries with it the most malignant possibilities is in the early stages of the illness, in which the relationship between denial of the existence of a lesion and delay in seeking treatment is of very considerable practical importance.

C. THIRD PHASE

First Step: Grieving.—The third phase, again, may be divided into two steps, an earlier one, of the expression of feelings of grief, and a subsequent one, of a readaptation by means of the assumption of new ego identifications, in which the painful information may be included in some manner. Although the identifications which serve as "vehicles" for behavior vary greatly in degree of maturity, they all have in common

the quality of including, rather than (as in the former two stages) excluding, the problem. Where the situation has to be precariously stabilized by the exclusion of information, the patient is constantly on the alert to keep the painful topic out of mind and consequently suffers from a considerable restriction of interest in the world in general; here, on the other hand, the potentialities of adaptation remain considerably more varied.

The expression of a feeling of grief with crying is a regular part of the process by means of which the prior adaptive identifications are abandoned and the new ones taken on. One patient described a violent reaction of depersonalization followed by a flood of tears (while visiting a neighbor) and a subsequent assumption of the idea that she had a year to live, an idea based on the history of another neighbor with a lesion similar to the patient's.

The mourning period is an essential step in reorientation in relation to the changed situation. To us, it appears that the grieving is a response to the loss of a whole system of assumptions and expectations upon which human beings build a view of the world. In some manner the weeping reaction displayed by the patient above serves to help "dissolve" the old system in such a way that it can be replaced by a new. Where the grieving is blocked for any reason, the patient has to adopt some precarious defensive sort of adaptation rather than attempting, after clearing the site, to make a new construction with the materials at hand.

We believe, further, from our experience with these patients, that the grieving reaction is possible only with a personality structure of a sufficient maturity and that it is greatly facilitated by the presence of a sympathetic listener. This listener supplies in the situation a predictable and nonthreatening human being who serves as a leader; the patient, in a human context because of his relationship to this supporting figure, can allow himself to experience and discharge tension in a disorganized way with some confidence in the prospect of being led back to safety with the help of the other person.

Second Step: Identification.—Since the emphasis in this brief communication is upon outlining the course of the recuperative process, we have not attempted to discuss at length the ways in which the ego identifications may themselves assume pathological significance. We may point out in passing that where the identification assumed by the patient is one the model for which is a relative or friend who has died of cancer, the hopelessness engendered by the assumed identity is a serious bar to treatment. Several patients mentioned that as soon as they knew they had malignant lesions, they thought there was no use doing anything about it, since "my father" or "the woman across the street" or "my sister" had had cancer and died of it.

Of the identifications which may be observed, there are as many separate possibilities as there are important figures in the life history of the individual, but, for purposes of description, we may separate out a few of what appear to be common types of identification which make it possible for the patient with cancer to construct for himself a life with some possibility of gratification. Three sorts which we have seen adopted with some success from this standpoint have been the assumption of the role of the good child, that of the physician, and that of the good parent, in an increasing scale of maturity. It, of course, goes without saying that to describe the process in any such fashion as this gives an entirely too structured and static impression of the kaleidoscope of events seen in dealing with a patient.

The first category, that of the good child, is well illustrated by a young woman with Hodgkin's disease. In spite of a great deal of difficulty with her family, it could easily be seen that she wanted very much to be good and to be approved of by them. In the early days of her illness, when the family first discovered the malignant nature of the lesion, the patient abruptly exchanged roles in her relationship to a younger sister: The direction of the relationship had been symbolized by gifts of clothes from patient to sister, but upon reception of the news, the patient took

to her bed and the sister brought her a negligee. The patient was told she had only a few months to live, and she and the family planned about this prognostication; when she lived on and on beyond the prediction, she became depressed and felt that she was a disappointment to them. In a series of interviews planned to help her to modify some of her attitudes, she demonstrated after some initial resistance a great enjoyment of the status of patient; so whole hearted was this reaction that she brought in all the other members of her family to the psychiatric clinic and she herself abandoned all other doctors. It was something of a problem to persuade her to be faithful to her appointments in the medical and tumor clinics.

In the second of the types of constructive identification mentioned above, that of identification with the doctor, there were two very prominent examples in this series. One of these was a woman who had survived a very long time after an operation for an ovarian cancer with metastases. In the interim she had devoted herself to reading about cancer and allied diseases and said there was little with which she was unfamiliar. She spoke in interviews several times of the unhappy fate of the poor doctors who had to get up early and work hard while she could take it easy in bed. The other patient had previously exhibited an adaptation on this basis in her profession of dental assistant, when she felt pleased if allowed to perform minor procedures under the supervision of the employer. In the hospital, she felt best when she was able to take care of the other patients; in several instances she accomplished a good deal with patients on the ward by interviewing them in a manner similar to that in which she herself had been interviewed.

In the third of these categories we have observed several instances of a really creative adaptation to the illness in patients who had solved for themselves the problem of dying. These patients had managed to accept the inevitable with cheerfulness and to direct their attention toward helping other patients and their own children to get through the difficult time. These patients had an inner security of such a nature that they did not need to borrow artificial status, as did the former patients. It was striking to note how much of a benign influence was exerted by one woman in the breast tumor clinic as she simply sat on the benches and talked freely to anyone who wished to speak to her. She said that she had decided since she was going to die she wanted people to remember her as a good person, and she presented this picture in a very effective manner.

COMMENT

The three phases which we have described above may be seen to be variations of a general statement a patient makes about his relationship to the threat: (1) "This is not me" (2) "This alien thing is no part of myself," and (3) "I have the wrong idea of myself and shall have to change it to get along." In terms of Freudian theory, the first phase is that of helplessness, or primary anxiety, and of the immediately succeeding response; the chaotic reaction appears to us indistinguishable from what Goldstein calls the "catastrophic reaction." The first step of the second phase corresponds to the "paranoid position" described by Mrs. Klein, with the denial representing, it seems to us, a version of the "manic defense"; the patient presents what Goldstein refers to as a "concrete attitude," in that he relates the information to some specific entity and then operates upon that entity as though it were the lesion. In the first step of the third phase we are reminded of Mrs. Klein's "depressive position"; the process involved is the internalization of the traumatic information, with the consequent destruction of the old idea of the self and the necessity of a reconstruction, a process of the formation of a new basic abstraction.

It is manifestly impossible to discuss in an exhaustive way the implications of the findings presented in this sketchy way. For the purpose of pointing up the suggestions we are interested in, we may confine ourselves to the second and third stages, representing, it appears to us, the processes of restitution which fall into what is described

in classic psychoanalytic terms as ego functioning.

The first of the four phases, that of projection, is of immense interest from several standpoints; it represents a developmental epoch in which the facts are interpreted by the patient in a solidified, concrete representation of a type which demonstrates the poor definition of the "ego boundary." The threat to the integrity of the concept of the self is met by the assumption that the dreaded fragment of the ego is a foreign or alien object introduced from outside and therefore in no way the responsibility of the individual himself. Especially to a cultural group with strong puritan leanings, this device is of great value in assuring the individual of his own blamelessness, and, moreover, it provides an explanation which satisfies to some extent the need for a satisfactory explanation of a puzzling situation.

This solution to the problem is a notably poor one, however, as repeated efforts must be made to ensure the separation of the alien portion which follows the individual as surely as his shadow. The foreign portion has been described under the general term of "bad internal object"; this term in itself is an abstraction which covers an immense variety of concrete manifestations at all levels of human functioning. Such a "bad internal object" is the "devil," of which the sick and the evil were thought to be possessed in primitive times; and, in community terms, the witches of Salem, who were executed in an effort to purge the community of evil thoughts and deeds.

In these patients of ours, the shifting referent of the bad internal object could be seen in a wide variety of manifestations; we were particularly interested in one salient observation, that of the identical process but inverse manifestation in patients with cancer and with cancerphobia. In cancer patients, as exemplified above, the individual sought in many instances to formulate the situation by transferring his concern from the somatic lesion in his body to the image of a distressing close relative, child, spouse, or parent in most cases, whereas the patient with cancerphobia maintained an uneasy relation to some relative by transferring his concern to an imagined lesion inside. The essentially abstract nature of the concept of the self is nowhere better illustrated than in this connection, since for the purposes of this mechanism of defense the image of the malignant relative is equivalent to the image of the malignant process.

To illustrate even further in an effort to clarify this difficult conception, we may cite some further material. One of these patients described the last illness of her father, in which he was suffering from a cerebral lesion which was characterized by convulsions and by a total inability to communicate with the family. The patient was horrified by her fantasies of his experience behind the immobile mask; she became unable to go into his room without a severe anxiety attack and after several days became totally aphonic. When he died, she was relieved of the aphonia and was able to care for the body without any great distress. She endeavored, if our interpretation is correct, on the one hand, to isolate herself from the uncontrollable alien person her father became in his nonhuman state, and, on the other, participated in his illness by her vicarious loss of voice.

Another patient, a severe borderline neurotic woman with an operation habit, attempted time after time to relieve herself of her internal object by means of surgical removals of various organs. She was fat, but she denied any responsibility for her obesity by saying she was not hungry, she merely was following the demands of an implacable stomach; she told of ideas of having something black and horrid inside her, like a tapeworm. After years of work with the problem, she remembered terrifying attacks of rage against her father, in which she wished to tear him limb from limb, when she felt that in urinating he purposely left the door open to taunt her with his possession of an organ she had been denied. Another woman with a similar problem described fantasies of "black brains" in her head and wondered if it might be the best treatment

to open her skull and scoop out the diseased areas. Both these women dealt with black things inside to avoid the intolerable effort of understanding themselves as persons capable of harboring murderous impulses against a parent.

The stage of simple denial is of less interest from a theoretical point of view because of the immensely reduced color in the material, as well as because of the reduced complications suffered by these patients, due to the relatively stable adaptive situation which is possible with a bland denial of the presence of the lesion. We suspect that the relatively emotionless denials of these patients are attenuated versions of the florid denials vividly seen in the "manic defense," in which the patient so flagrantly states his ideas of his own importance and happiness. We have not seen in our series, but have heard reported by surgeons with a wide experience, cases in which the patient in a terminal phase displayed great hopefulness, which we suspect is similar to the spes phthisica which used to be observed in terminal cases of tuberculosis.

The depressive position is of the utmost importance in the restitution of the ego because of the necessity of "vacating" a previous state of adjustment before it can be filled by a successive state. One of the most impressive aspects of this state is the severity of the anxiety which accompanies the emptiness. It appears to us that it is the intolerable character of this depressive anxiety which makes the patient think of suicide as a quick and certain method of terminating the suffering. (A very large proportion of patients have reported that at the moment of learning of the diagnosis, or in anticipation of learning it, suicide appeared to be a useful solution.) It may be noted here that a great paradox occurs, in that it is the inclusion within the idea of the self of the alien, foreign, intolerable object which leads to the sensation of emptiness; we believe it possible to resolve the paradox by noting that the emptiness is observably an inability to act or to plan action: The emptiness is one of purpose. The individual becomes aware of himself as including entirely new and alien potentialities, and so immense is this inclusion that none of his previous patterns of action can be carried out without an initial period of hesitation and checking on possibilities.

Finally, in the new adaptation made possible by a novel ego identification, the patient fills in the emptiness in his action pattern repertory by some sort of view of himself which includes the new, initially traumatic, information and begins to go about his business again in some manner. As we have noted above, it is usually easily evident afterward from whence the new action pattern has been derived, although it is frequently difficult or impossible to predict in advance which of the many models available to him the patient will select as the appropriate one for him, and it is equally difficult to say in advance whether the new ego identification will offer a method of gratifying the human needs of the individual. This reconstruction of an ego, or of a self-concept, or of a useful repertory of behavior patterns, to put it in a variety of ways, is an enormous achievement in abstract thinking and planning.

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Semen Dyscrasia in Schizophrenia

M. LEOPOLD BRODNY, M.D., Boston

Frontiers exist between the various fields of medicine, but modern research is gradually eliminating them by adapting the diagnostic tools of one specialty to investigate another. This report is an example of such an effort and is the application to psychiatric patients of techniques which were originally devised for determining male fertility.

An unexpected opportunity arose to study semen quality in a group of schizophrenic patients. Observations were to be made on the chemistry and morphology of the ejaculatory secretion following ultraviolet irradiation of body surfaces. Patients in a mental institution were the subjects, and among those selected, seven men were found unsuited to the study. It became apparent from observations made on specimens obtained as controls prior to irradiation that their semen analyses differed from those of other psychiatric patients and from those of mentally normal men observed in an infertility clinic. Each member of the disqualified group had been diagnosed as schizophrenic by the hospital staff long before this investigation was undertaken, and had been under continuous hospitalization for upwards of three years. There were no schizophrenics in the group whose control specimens were found to be acceptable for the study.

It is generally recognized that a low fertility is common in schizophrenia, but a review of pertinent literature failed to reveal any significant study of the ejaculatory fluid. An important reason for this failure is the task of obtaining specimens. Blood, which is one of the most frequently examined body fluids, is easily obtained by venous puncture and can be frequently procured in comparatively good quantities. Semen, on the other hand, is only obtained by coitus interruptus or by masturbation, is usually limited to 3 or 7 cc. per specimen, and cannot be too frequently obtained from the same patient without disturbing its morphology and biochemistry. The procurement of semen also presents emotional and religious problems.

None of these difficulties is insurmountable. Workers in the field of sterility have reported semen studies on series of hundreds of cases. The important point in obtaining these specimens was the motive for the procedure. Cooperation was forthcoming when the physician explained the potential value of semen studies in infertility. Patients are entitled to any examination which might help in the diagnosis of their difficulties.

This is especially true in the mental patient if the possible organic etiology of a psychiatric disease is to be studied. The semen is a sensitive indicator of disturbed body physiology and is as deserving of investigation as any of the other body fluids. To limit the indication for semen analysis to the fertility phase would hinder scientific progress. Medicine would certainly have suffered seriously if we had examined blood only on the basis of its primary functions and had neglected the changes which diseased organs produced secondarily in cell morphology and biochemistry.

The histology of the testes in schizophrenia was investigated early, because of the possibility of an endocrinopathic etiology and the symptomatic prominence of sexual dysfunctions. Mott,[16] as early as 1919, studied the gonads of schizophrenics at autopsy and recognized the occurrence of gonadal failure. His findings and interpretations were distorted by local terminal changes and by the systemic effect of the intercurrent disease of which many of the patients had died.

From the Department of Urology, Boston State Hospital, and Beth Israel Hospital.

Testicular biopsy, which was primarily devised for the study of male sterility, was adapted by Hemphill * to investigate the gonadal status of schizophrenics. He obtained specimens of testicular tissues at all stages of the disease, including the periods of remission, and noted microscopically varying degrees of testicular atrophy in the majority of the nonparanoid schizophrenics, but not in other mental patients. The pathologic changes were present even in the young patients and were characterized by hyalinization of the basement membrane, by defective germ plasm with arrested spermatogenesis, and by tubular destruction. These lesions were irreversible by therapy with follicle-stimulating hormones.

Blair and associates performed testicular biopsies on 27 schizophrenics and reported contradictory results in that not a single biopsy specimen of this group was considered pathological and without exception all specimens had tubules, tunica propria, and Leydig cells within normal limits. Except in one case with inflammation, mature sperms were found uniformly and in normal quantities. The pathologist of this team felt that neither the frequency nor the degree of changes which he noted were any greater than would be expected in a similar group of entirely normal male patients.

The marked difference in the observations of these two competent groups of observers is disturbing, but similar divergencies have occurred in other studies made on schizophrenics. The etiology of schizophrenia is obscure, and it is possible that we are not dealing with a clinically homogeneous group. Schizophrenia has not only fluctuating psychopathologic symptoms but an inconstancy of biochemical variations which prevent the establishment of any characteristic patterns.

Biopsy of the testis is a useful procedure but has many limitations. Biopsy specimens are minute, show only a small section of the entire testis, and are difficult to interpret physiologically. One cannot assume that pathologic alterations observed in a small area of the testis are universally present throughout the organ. Engle † has emphasized the importance of correlating changes in structures with changes in function. "The greatest difficulty with testicular biopsy lies in relating the histologic diagnosis of the specimen to the semen analysis." Also, with testicular biopsy there is no opportunity to study biochemical changes in the semen.

* References 11 and 12.

† References 3 and 4.

TABLE 1.—*Semen Analysis for Seven Schizophrenic Patients*

	Catatonic				Paranoid		
Age	31	34	48	23	34	26	32
Patient	W. P. M.	A. G.	H. E. P.	T. S.	V. Z.	R. J. S.	H. S.
Volume, cc.	3.0	4.0	3.8	4.0	3.1	2.4	2.0
No. cells, million/cc.							
Active cells/cc.	52	93	1	70	17	113	87
Inactive cells/cc.	28	55	12	25	13	50	23
Total cells/cc.	80	148	13	95	30	163	110
Activity, %	65	62	7	73	56	69	79
Total active cells	156	372	3.8	28	52.5	271	174
Abnormal, %	68	65	70	77	20	37	18
Round	5	1	2	3	—	3	—
Pin	1	—	—	3	—	—	1
Giant	1	1	—	—	—	1	1
Tapering	4	3	5	3	3	8	1
Amorphous	57	60	63	67	17	22	15
Duplicate	—	—	—	1	—	3	—
Sugar, mg./100 cc.	170	182	—	350	186	330	418
Marital status	Single	Single	Single	Single	Married, with two children	Single	?

METHOD OF COLLECTING SPECIMEN

Semen specimens were collected by masturbation in clean, dry, wide-mouth glass bottles by a method similar to that employed when appraising male fertility. The five-day period of sexual abstinence prior to the examination could not be observed, owing to the difficulty in controlling the frequency of masturbation of schizophrenics. The motility of the sperms were noted within two hours, and the remainder of the examination was done the same day.

METHODS OF ANALYSIS

The sperm counts and estimations of motility were done according to the method of Farris,‡ and stained smears were made according to the technique of Greenberg.[10] The classification of morphologic types of sperm cells devised by Hotchkiss [13] was used in this study. Hyaluronidase was determined by the methods of Werthessen and associates.[19] Sugar determination was also performed by the standard method of Folin. The findings are classified in Table 1.

PHYSICAL CHARACTERISTICS OF EJACULATE

There was no loss of ejaculate in these specimens, since they were all obtained by masturbation under supervision. The amount of fluid produced in each ejaculation by the schizophrenic compares in quantity with the mean volume of 3.33 cc. reported by MacLeod [15] in his study of the semen of several hundred fertile men. This finding is significant, since these volumes remained unaffected even though these patients had masturbated frequently (once or twice daily) for a long period of time (years). No differences were noted in the viscosity, color, or odor of these specimens as compared with that of normal men.

BIOCHEMICAL ANALYSES

Quantitative determinations of hyaluronidase were performed on the semen of the schizophrenics and were within the range of normality observed in fertile men. Apparently the factors producing the defective cytology had not changed the amount of this enzyme in the ejaculate. The absence of any relationship between the quantity of hyaluronidase and the presence of a high percentage of abnormal sperm forms is similar to observations in the mentally normal patient.

No significant variation of the sugar content of the ejaculate was observed.

MOTILITY

The spermatozoa in all the specimens but one had a motility index of over 50%. This compares favorably with the results reported by Falk,[5] who found an average of 61.4% of active cells at the end of three hours in the ejaculate of a group of 100 men of repeatedly proved fertility. The combination of a high incidence of abnormal spermatozoa with a high percentage of motile sperms is not unusual. It is generally recognized that the highly abnormal spermatozoa may be motile but that this factor does not necessarily indicate its fertilizing capacity. These abnormal spermatozoa, however, do not demonstrate the characteristic motility of the normal cell but move sluggishly, and often in a rotary or oscillatory manner.

TABLE 2.—*Classification of Spermatozoa in Percentages*

Hotchkiss, Percentage		Farris, Percentage
	Normal	
89.8	.....	88.0
	Abnormal	
0.6	Giant	0.9
3.6	Tapering	0.3
0.6	Pinhead	1.0
1.6	Round forms	0.3
1.84	Duplicate	1.0
2.1	Amorphous	8.5

SPERMATIC CYTOLOGY

Table 2, presented for comparison, represents the findings by two investigators based on semen analyses of men whose wives conceived during the period the husbands were under study. The most striking finding in the semen of the schizophrenic is the high incidence of spermatic abnormalities, especially of the amorphous forms. It is impossible to tell whether these abnormal cells represent atypical immature forms or spermatic monstrosities.

‡ References 6 and 7.

Little is known about the factors which produce abnormal sperm forms. Engle § had noted developmental abnormalities of the tubules in some of the testicular biopsies performed on patients with a high percentage of abnormal spermatozoa but was unable to account for their occurrence. Olesen,[17] after extensive study of spermatic morphology in semen and testicular biopsies, concluded that the incidence of abnormal spermatozoa did not increase with advancing age. Chang produced abnormal spermatozoa in rabbits by cooling the testes and epididymis. Spermatic dysplasia has also been observed in malnutrition, vitamin deficiencies, exposure to toxic chemicals, such as nitrogen mustard preparations, and after irradiation.

Schizophrenics manifest many endocrinologic, metabolic, and nutritional disturbances, which in themselves might influence spermatic cytology. It is therefore difficult to assign definite responsibility to a single cause for spermatic dysplasia in a disease in which there are so many etiologic considerations.

ENDOCRINE FACTORS

The status of the thyroid-gonadal relationship is not entirely settled even in the mentally normal male. There are clinical and experimental evidences which suggest that a minimal thyroid function is necessary for normal spermatic efficiency, but whether the mechanism is direct or indirect or both is not known. Extremes of thyroid dyscrasia affect the maturity and motility of the spermatozoa, but there is no change in spermatic cytology as observed in the schizophrenic.

Recently much attention has been focused on the adrenal secretions and on physiologic substances which produce psychologic disturbances similar to those of schizophrenia. Some of these compounds have hallucinatic properties, produce EEG changes, and inhibit the brain respiration. It will be of interest to note whether these drugs also produce changes in spermatic cytology similar to those we have observed in schizophrenics.

§ References 3 and 4.

17-KETOSTEROIDS

The 24-hour 17-ketosteroid excretion is related to the function of the testis and the adrenal. Its determination is useful as an index of their hormonal activity. An attempt to correlate the abnormal spermatic cytology with the 17-ketosteroid excretion of the schizophrenic was futile. The only point that can be emphasized is that there is an excretory variation. Hemphill || found that cases of schizophrenia that appeared to be clinically identical, of approximately the same age and duration of illness, had quite different patterns of sex hormone excretion. The only common factor he noted was a variability of the endocrine system, so that while in normals or in patients with other mental illnesses the daily output of sex hormone factors may be constant, in individual cases of schizophrenia the daily or weekly variation may be extreme.

On the basis of some as yet unpublished findings, the following observations have been made: The 17-ketosteroids are elevated in the patient with acute schizophrenia. They subside when the patient's mental symptoms improve. The 17-ketosteroids are low in chronic schizophrenia. In schizophrenia there is a loss of the stress mechanism; the patient fails to react to many stimuli, including epinephrine. The first sign of recovery is the return of the stress mechanism. In chronic schizophrenia there is possibly a type of adrenal cortex exhaustion.

It is to be noted that even though spermatic dysplasia has been observed both in testicular biopsies and in semen analysis at a very early age, the schizophrenic has sufficient androgen to develop and to maintain normal-appearing sexual organs. It is also to be noted that the spermatic cytology of mentally normal men with either elevated or diminished excretion of their 17-ketosteroids observed in the fertility clinic does not show the high incidence of abnormal forms observed in the schizophrenic.

Many other factors exclusive of an endocrinopathy could disturb the morphology of

|| Hemphill, R. E.: Personal communication to author.

the spermatoza in the schizophrenic. Bagney and Norris [1] studied the nutrition of mental patients and found that 374 schizophrenics after eight years of hospitalization showed a 50% greater incidence of underweight than did the total hospital census. There is the possibility that a coexisting proteinemia or avitaminosis is responsible for the change. However, most clinicians believe these factors exert only a minor effect on human spermatogenesis except in actual debilitation.

There is also the question of physical exertion as an etiologic factor. Farris studied the ejaculatory fluid obtained from athletes fatigued by a competitive game and found that acute physical exertions did not produce any significant change in their semen analyses. I am unable to find any scientific report on the effect of chronic physical or mental fatigue on semen specimens.

The effects of frequent masturbation on the production of abnormal forms must also be considered. We have had the opportunity of examining the ejaculatory fluid of many chronic masturbators but have not noted the excessive incidence of abnormal forms present in the schizophrenic. Farris studied the effects of daily ejaculation for 20 consecutive days on the characteristics of the specimens and noted that the per cent of normal forms was not affected by the frequency of ejaculation. Hotchkiss noted a marked drop in the cell count after frequent intercourse, but the incidence of the morphologic types of spermatozoa was relatively unchanged.

There is some evidence that a toxic substance is present in schizophrenia. Fischer recently studied the degree of toxicity of schizophrenic serum by determining the mortality of larvae in a medium of serum in water. He noted a striking difference of toxicity if the serum of acute untreated schizophrenia is tested and compared with the serum of normal volunteers. The seminiferous epithelium is very sensitive to toxins, and this factor may be sufficient to produce a disturbance of the germ plasm. Gjessing [8] has described a selected group of schizophrenics with periodic abnormal retentions of nitrogen. Fischer and associates observed disturbances of the detoxicating function of the liver in the course of schizophrenic attacks. They found that changes in the liver function appeared together with the schizophrenic psychosis and reasoned that the former was due to a generalized intoxication.

This mechanism may be indirect, since the liver plays an important role in the inactivation of estrogens and androgens. Impairment of liver function to any marked degree is often associated with diminished amounts of urinary 17-ketosteroids. Glass [9] noted impaired spermatogenesis resulting from experimental cirrhosis, and in humans observed that striking testicular atrophy often occurs with cirrhosis of the liver. The mechanism is a failure to inactivate estrogen, which, being free, tends to affect and injure the germinal epithelium. However, the effect of estrogens on spermatogenesis is to cause germinal hypoplasia and a lowered sperm count. The production of the schizophrenic type of germinal dysplasia has not been observed with either estrogen or androgen therapy. There is the possibility that an X substance exists.

THEORY OF ENZYMATIC ACTION

Spermatogenesis is a metabolic process under hormonal control, but the actual mechanism of the production of sperm through the various stages of development to the final mature sperm cell is a series of competitions of enzymes and antienzymes. The testis is a very sensitive organ, and its function is rapidly and easily affected by many disturbances in the physiology of the whole organism. The deficient spermatogenesis of alcoholism, avitaminosis, and malnutrition is probably due to an imbalance of catabolic and anabolic enzymes. The arrest of spermatogenesis observed with thyroid, pituitary, or adrenal insufficiency may be due to the decrease of production of a single enzyme or to enzyme inhibition.

Spermatogenesis not only may be arrested, but may be deviated. Foreign enzymes produced by roentgen irradiation or parenteral administration of nitrogen mustards or exposure to toxic chemicals, etc., may cause

alterations in the spermatic structure which are not observed in any stage of the normal maturation pattern. It is possible that in schizophrenia the disease disturbs the mechanisms of enzymes so as to produce a spermatic deviation, rather than an arrest or a deficiency.

SUMMARY AND CONCLUSIONS

Schizophrenics manifest many systemic disturbances of their physiologic functions.

The semen and its cytology are sensitive to general physiologic changes and are as deserving of study as any of the other body fluids.

The number of seminal analyses reported are too few to permit any conclusions as to either the genesis of schizophrenia or the etiology of spermatic monstrosities.

The results suggest the presence in schizophrenia of an X substance, which deranges spermatogenesis and produces the appearance of abnormal forms of spermatozoa.

636 Beacon St. (15).

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Experimentally Induced Hypotension

Clinical and Electroencephalographic Consequences

HAROLD STEVENS, Ph.D., M.D.
and
JOSEPH F. FAZEKAS, M.D., Washington, D. C.

The neurologist is frequently confronted with the problem of syncope and with determining its etiology. Postural hypotension is a possible cause that is considered only rarely in this connection, and the neurological literature is scanty on this subject, although many articles have appeared since its description in 1925 by Bradley and Eggleston.[1] It is of further interest that neurological disease may be the primary disorder responsible for the orthostatic hypotension, e. g., syphilis of the central nervous system or syringomyelia.

The objective in this investigation was to devise a reliable and reproducible method of effectively, promptly, and safely producing a controllable hypotension, and to observe the associated clinical and electroencephalographic changes. Previous studies[2] had demonstrated the efficacy of the technique of placing a subject on a tilt table, injecting hexamethonium intravenously (1 cc/min. of a 2% solution), and raising or lowering the head of the table to obtain the desired response. Under such controlled experimental conditions it would be expected that vasodilatation abetted by gravity would cause peripheral pooling of blood, a decreased venous return, diminished cardiac output, and consequently a reduction of cerebral blood flow. Since any degree of tilt of the patient's head could be produced, the extent and rapidity of the induced hypotension were correspondingly under ready control. The combined use of intravenous hexamethonium and elevation of the head was uniformly effective in producing profound hypotension in 19 experimental subjects. Two additional subjects with spontaneous postural hypotension were also studied.

Simultaneous EEG records and, in a few instances, cerebral blood flow studies were made in normal subjects and in patients with various disorders. A six-channel Grass electroencephalograph recorded the brain waves in the conventional manner. Twenty to 60 mg. of hexamethonium chloride was injected, and serial recordings of blood pressure were made directly from the femoral artery with a damped aneroid manometer[3] as the head of the tilt table was progressively elevated. Cerebral blood flow measurements were made according to the method of Kety and Schmidt,[4] as modified by Scheinberg.[5]

CLINICAL OBSERVATIONS

The clinical phenomena observed during the rapidly induced hypotension were more or less stereotyped. The subject developed a sequential pattern of signs, usually beginning with slight pallor, then sweating. A subjective and objective state of relaxation was observed in most cases, but in a few subjects marked anxiety and restlessness appeared at the stage of sweating. On the contrary, many patients, apprehensive prior to the induction of hypotension, became quite composed and reported on being questioned, and also spontaneously, a feeling of lassitude and equanimity. With increasing hypotension, sighing respiration and then frequently yawning were manifest. At this stage the subjects were alert and oriented and usually

From the Department of Neurology, George Washington University School of Medicine and the District of Columbia General Hospital.

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answered readily and appropriately. There were no pupillary changes, and extraocular movements were of full range and were normal. The subjects sometimes complained of dryness of the mouth and dizziness. The former symptom may be due to the drug per se and not to the hypotension. Further depression of blood pressure produced staring and fixity of expression, often followed by coma or by abrupt onset of convulsions, which were usually mild and generalized. Occasionally the seizure was unilateral. Brief twitches of the face and circumoral region or of the limbs sometimes preceded the convulsions.

In several instances amblyopia or marked blurring of the vision occurred, causing the subject to call out in a frightened manner. The alarm was shared by the experimenters, and these patients were promptly placed in a head-down position. In all instances the subjective and objective changes with hypotension were quickly removed by tilting the patient to a head-down position. If the patient sat up of his own volition, brief syncope would occasionally ensue. Many patients remained relaxed and composed up to two hours after the resolution of the acute stages of the experimental hypotension.

Since convulsions frequently developed in these subjects, it occurred to us that we might employ this technique in treating psychiatric patients as a substitute method for electroconvulsive therapy. Although the production of the hypotensive type of convulsion is more complicated, one particular advantage in this technique occurred to us, namely, that the convulsion was always mild, and fairly gradual in onset, and thus the likelihood of fractures was eliminated. The increasing amount of litigation stemming from fractures sustained during electroconvulsive therapy further justified the exploration of this procedure.

It is generally conceded that, regardless of how the seizure is produced, that is, by camphor derivatives, electric current, etc., benefit from the convulsion itself is the common denominator. Thus, if seizures can be precipitated by hypotension, similar therapeutic results might be expected. In addition, many hold that cerebral anoxia is the modus operandi for the improvement following convulsive therapy. In this connection, it is quite possible that cerebral ischemia without a seizure might be beneficial and is thus similar to the mechanism in nonconvulsive therapy, such as insulin treatment. This area deserves further exploration.

With the simultaneous use of hypotensive drugs with the tilt table, the resulting cerebral ischemia is under prompt and easy control of the operator, in contrast to the predicament in electroconvulsive therapy, where after the circuit is closed the convulsions cannot be influenced or terminated.

A depressed middle-aged woman was selected for treatment because she fulfilled the usual criteria for convulsive therapy. She was retarded and showed poverty of interest and paranoid elaborations. She refused to eat, had lost weight, and was sleepless. She was given intravenous hexamethonium; her head was elevated on the tilt table, and her blood pressure dropped to critical values. The patient had a brief convulsion. The following day she was much more communicative and ate without urging. Only two more treatments were given because the patient left the hospital. Two other patients with catatonic schizophrenia were given one treatment each, but without any significant change in their clinical status. Further studies are in progress to investigate the potentiality of this technique.

Because of the observed relaxation occurring in the hypotensive state, its effect on four subjects with advanced senile Parkinsonism was determined. In all instances extrapyramidal activity was abolished only when the blood pressure was reduced to critical levels and returned immediately with a rise in pressure. Relief of muscle spasm was also noted in a subject with hemiparesis resulting from an old thrombosis of the middle cerebral artery. During the time when signs of cerebral ischemia were manifest, there was marked relaxation and flaccidity of the muscles of the left arm. There was no lasting effect, the spasticity returning with a rise in pressure.

ELECTROENCEPHALOGRAPHIC CHANGES

The EEG was studied in 21 patients hospitalized at the District of Columbia General Hospital. Tracings were run before, during, and after hypotension was induced. Because of the activity of the patient and of the experimenters near him, artifacts contaminated parts of the record in many instances.

It was surprising to observe that the EEG did not reflect *pari passu* the falling blood pressure but, rather, in general maintained a normal, although slightly altered, pattern, even in the face of sustained hypotension. However, when the pressure had fallen beyond a certain critical level, the EEG changed abruptly and often anticipated by a few seconds coma and convulsions in the subject. This maintenance of a normal EEG pattern under these conditions of acutely imposed hypotension suggests that some protective reflex accommodation takes place in the vascular physiology of the brain which decompensates suddenly when the limits of adaptation are reached.

As stated, dysrhythmia appeared only after a profound drop in blood pressure. However, in many instances, changes within normal limits appeared during the stage of declining blood pressure. In most instances these

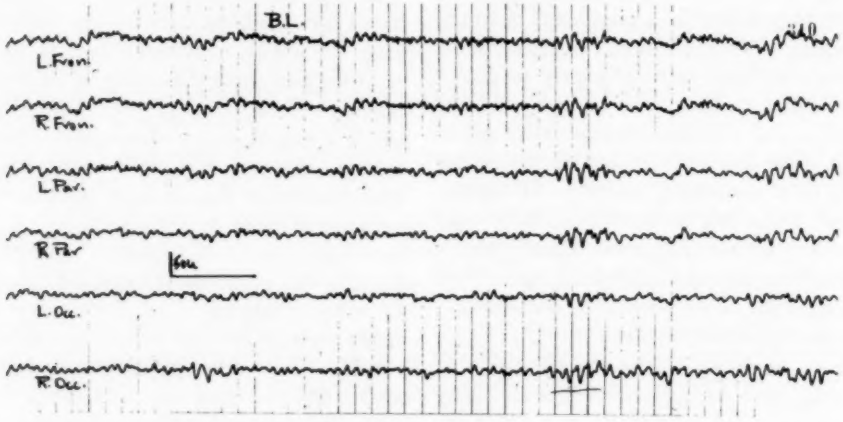

Fig. 1 (B. L.).—Paroxysmal dysrhythmia characterized by 6 per second square waves. Initial blood pressure, 170/110.

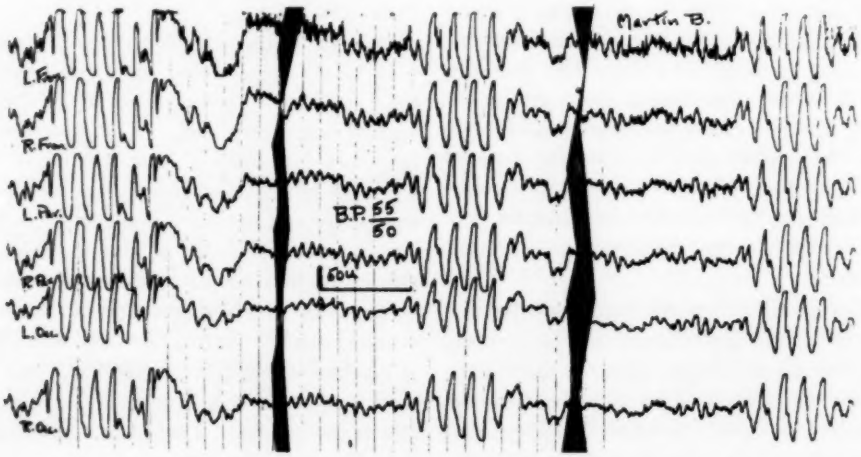

Fig. 2 (M. B.).—Three consecutive EEG specimens with blood pressure 55/50, in a normotensive subject.

changes consisted of slowing activity to 8 to 10 per second, with slight increase in amplitude.

The initial pressure and the rate of decline of the blood pressure are two variables that may influence the clinical and EEG response to hypotension.

A variety of dysrhythmic patterns emerged. One was illustrated by Patient B. L., age 55, whose initial pressure was 170/110 and whose mean arterial pressure was 135 mm. Figure 1 is a specimen from her EEG record showing paroxysmal bursts of 6 per second square waves, appearing over a period of five minutes of declining pressure, which reached a nadir of mean arterial pressure of 40 mm. Synchronous bursts of these waves continued for five minutes after the patient was restored to a horizontal position. Normotensive subjects in general showed similar clinical and EEG changes, with the induced hypotension, however, usually at lower pressure levels. Figure 2 illustrates three consecutive representative samples of the EEG of such a subject. High-voltage slow waves appearing at a blood pressure of 55/50 presaged the imminence of a convulsion, and the patient was quickly returned to

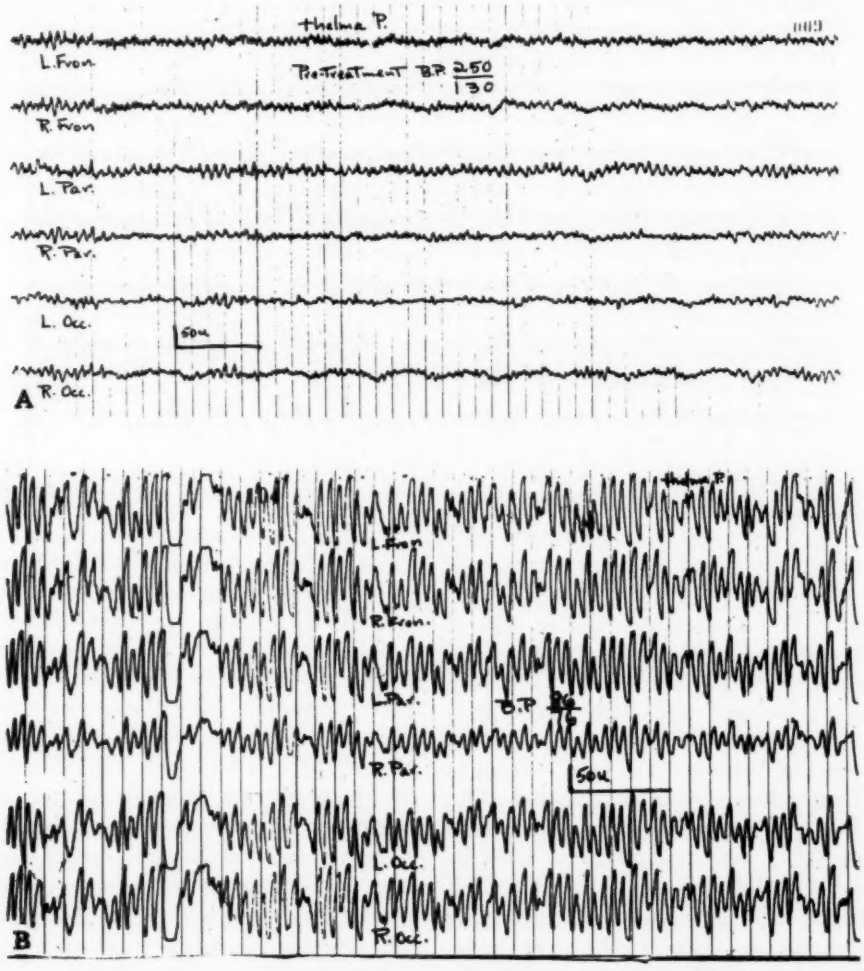

Fig. 3 (T. P.).—Pretreatment tracing (*A*) and with induced hypotension (*B*) in a hypertensive subject.

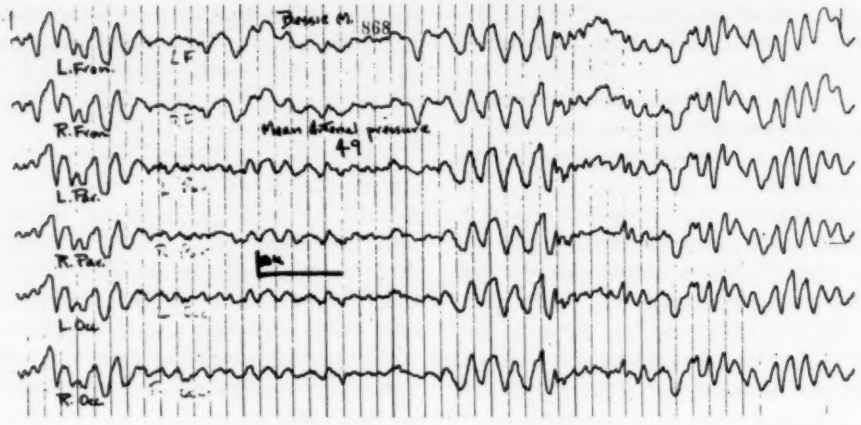

Fig. 4 (B. M.).—Paroxysmal slowing followed by convulsion. Initial blood pressure, 170/110.

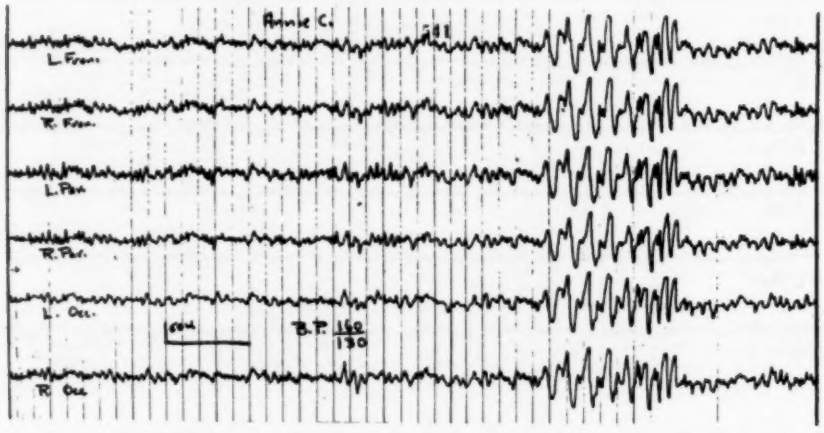

Fig. 5 (Annie C.).—Specimen of paroxysmal spikes invoked in a known epileptic by induced hypotension.

the horizontal plane. These slow waves gradually resolved over the next four minutes.

Case T. P. demonstrates another type of dysrhythmia precipitated by hypotension. Figure 3*A* shows a representative specimen of the pretreatment EEG, with a blood pressure of 250/130. Figure 3*B* shows the EEG after the blood pressure had been lowered to 86/76 after 36 mg. of hexamethonium chloride had been given. A grand mal seizure ensued, which was promptly terminated by tilting the head down.

Another type of dysrhythmic pattern is demonstrated in Case B. M. The initial blood pressure of 170/110, measured by the cuff manometer, corresponded to an initial mean arterial pressure of 135 mm. The latter was decreased to zero with the patient tilted at a 45-degree angle. At this point a grand mal seizure occurred. Figure 4 represents the EEG pattern during the period of declining blood pressure. The tracing immediately prior to this was normal, the patient complaining only of dizziness. Restitution of consciousness was prompt, but the EEG continued to show paroxysmal bursts of high-voltage, regular, slow waves for 12 minutes after the seizure, at which time the mean arterial pressure was 60 mm. This suggests that although the defenses against hypotension are overwhelmed abruptly, physiological recovery from such hypotension-induced

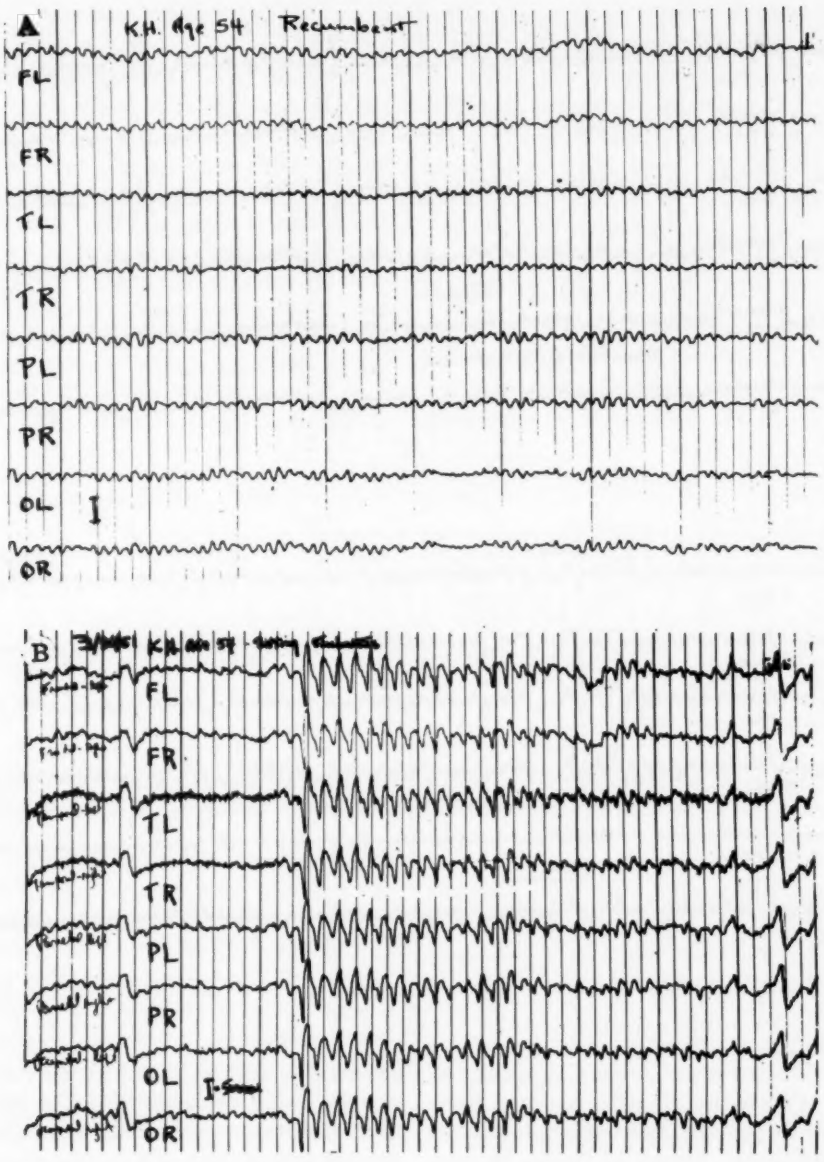

Fig. 6 (K. H.).—Specimen of record in the recumbent (*A*) and in the sitting position (*B*). Convulsion followed. No drug used.

seizure is slow. This phenomenon might reflect an accumulation of metabolites during the period of hypotension.

Of the 21 patients, 1, Annie C., may have been epileptic. Her EEG was a borderline abnormal one. The resting blood pressure was 230/160. After administration of a total of 50 mg. of hexamethonium chloride, the pressure dropped to 160/130 and paroxysmal spikes and slow waves appeared (Fig. 5). These were not associated with any significant clinical change. Pressure was further decreased to 140/110 by further elevating the patient. The same generalized paroxysmal dysrhythmia continued without clinical manifestations.

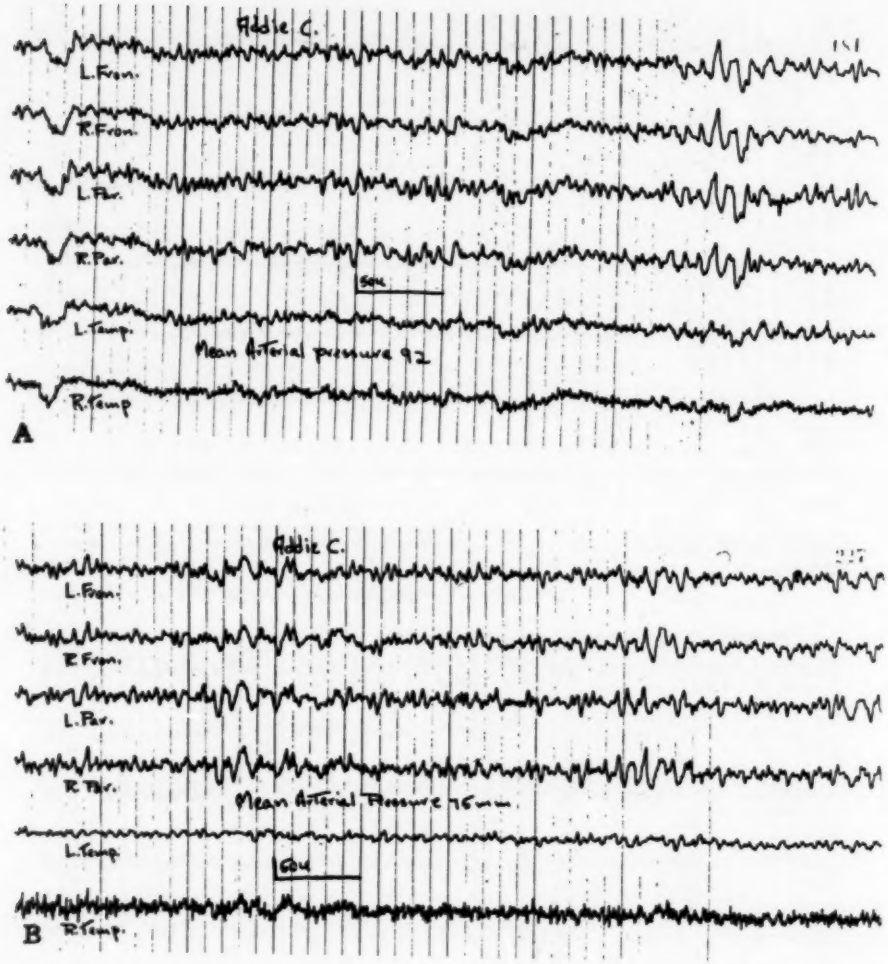

Fig. 7 (Addie C.).—Paroxysmal slow waves at mean arterial pressures of 92 mm. (*A*) and 75 mm. (*B*).

The EEG pattern of Annie C. is similar to that of Patient K. H., who suffered from spontaneous postural hypotension associated with convulsions. Figure 6*A* typifies his record during recumbency, and Figure 6*B* demonstrates a typical paroxysmal burst that appeared five minutes after the patient was placed in a sitting position. No hypotensive or other drug was used to induce the fall in blood pressure and the ensuing convulsion. Addie C., another patient with spontaneous postural hypotension, exhibited a dysrhythmia during the pretreatment control period. The abnormality in the EEG appeared to be accentuated, with reduction of her pressure, by only tilting the table (Fig. 7*A* and *B*). Cerebral hemodynamic studies were obtained on this patient and will be elaborated on further.

These observations suggest that acute hypotension, no matter how produced, might increase susceptibility to seizures. Also, these observations demonstrate a new technique of activation of the EEG which might be applicable in the investigation of patients with suspected focal or nonfocal epilepsy. This potential use of hypotensive drugs is being studied further.

CEREBRAL BLOOD FLOW

The energy required for the maintenance of the electrical activity of the central nervous system is derived for the most part by oxidative processes. The delivery of oxygen and glucose required by the cerebral cells for maintenance of their metabolic activity is dependent on an adequate cerebral circulation. Previous studies [2] have demonstrated that with an acute reduction of pressure the critical rate of cerebral blood flow, i. e., the rate at which signs and symptoms of cerebral insufficiency usually become manifest, is approximately 30 cc. per 100 gm. of brain per minute. The mean arterial pressure at which cerebral insufficiency develops varies considerably and appears to be related to the cerebral vascular resistance. It would appear that with an acute reduction of pressure the cerebral cells can extract sufficient oxygen from the circulating blood despite a significant reduction in the rate of cerebral blood flow. This is evidenced by the increase in the cerebral arteriovenous oxygen difference and the unchanged cerebral metabolic rate noted with an acute reduction of mean arterial pressure. If, however, the rate of cerebral blood flow is reduced beyond the level at which compensatory mechanisms become inadequate, energy production by cerebral cells promptly diminishes. It is at this critical point that changes in the electrical activity of the central nervous system become evident.

The Table presents the cerebral hemodynamic changes of two subjects—Addie C. and B. M., in whom cerebral vascular insufficiency was acutely induced. Patient Addie C., whom we previously mentioned, had idiopathic postural hypotension. In Subject B. M. hypotension was induced by hexamethonium. For both subjects, the data show an increase in the cerebral arteriovenous oxygen difference with a concurrent fall in the mean arterial pressure. The calculated values for cerebral blood flow show a progressive reduction toward critical levels. The variation in mean arterial pressure at which cerebral insufficiency may develop is also evident from the data.

Effect of Hypotension on Cerebral Hemodynamics and Metabolism *

Subject	Condition	MAP	CBF	$CAVO_2$	$CMRO_2$	Minutes Tilted at 40°
A. C.	Postural hypotension	110	60.3†	4.68	2.8	0
		80	53.8	5.20	...	24
		60	39.8	7.04	...	42
		45	35.3	7.94	...	52
B. M.	Induced hypotension	178	77.8†	3.52	2.7	0
		106	34.6	7.81	...	8
		72	34.3	7.87	...	10
		68	32.4	8.34	...	11.5

* In this table, MAP signifies mean arterial blood pressure, in millimeters of Hg; CBF, cerebral blood flow, in cubic centimeters per 100 gm. of brain/min.; $CAVO_2$, cerebral arteriovenous oxygen difference, in volumes per cent, and $CMRO_2$, cerebral oxygen consumption, in cubic centimeters per 100 gm. of brain/min.
† Determined values. Other values for CBF calculated by assuming constant $CMRO_2$.

SUMMARY

An effective and controllable means of producing hypotension was employed to study the clinical electroencephalographic and cerebral vascular changes in 21 subjects.

Profound and rapid fall in blood pressure is possible without producing significant EEG changes.

Beyond a certain critical level, dysrhythmia appears abruptly and is usually correlated with conspicuous clinical signs of cerebral ischemia and also with lowered blood flow.

The cerebral blood flow, and not the initial blood pressure or the decrement in blood pressure, is the determining factor in producing EEG changes. In subjects with severe hypertension, cerebral blood flow diminishes to critical levels at a relatively higher blood pressure. This is presumed to represent in-

creased cerebral vascular resistance and reflects a diminished capacity to adapt to the induced hypotension, as contrasted with normotensive or mild hypertensive subjects.

The clinical effects of cerebral ischemia produced in this way evoke a more or less stereotyped sequential pattern, which terminates in some instances in convulsions or coma. Decreased cerebral blood flow and electroencephalographic dysrhythmia occur abruptly and only after profound fall in blood pressure. The clinical manifestations may be conspicuous without any effects on cerebral blood flow or on the EEG.

The occurrence of cerebral ischemia with or without convulsions suggests that this technique of experimentally induced hypotension might duplicate the therapeutic response that occurs with other forms of convulsive therapy, for example, electroshock and pentylenetetrazol (Metrazol) shock. The hypotensive technique has the one advantage of producing milder and controllable seizures.

Another potential use of induced hypotension is in activation of the EEG.

Dr. Frank A. Finnerty Jr. and Dr. Jack Kleh gave aid in this study, and Mr. G. Edward Smith and Mr. William K. Young gave technical assistance.

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Stimulation of Suprabulbar Reticular Formation

Effect on Elements of Spinal Reflex Pathways

FRANS KLEYNTJENS, M.D.
KIYOMI KOIZUMI, M.D.
and
CHANDLER McC. BROOKS, Ph.D., Brooklyn

The effects of stimulating the suprabulbar or bulbar reticular formation on reflex activity of the spinal cord have been studied by Lloyd * (1941, 1944), Magoun † (1944, 1950), Rhines and Magoun [26] (1946), Bach [2] (1950), Austin [1] (1952), Lindsley [14] (1952), and numerous others. The parameters of bulbar and suprabulbar facilitatory and inhibitory areas have been well worked out (Lindsley,[14] 1952; Lindsley, Schreiner, and Magoun,[15] 1949; Magoun and Rhines,[23] 1946; Niemer and Magoun,[25] 1947; Rhines and Magoun,[26] 1946), and the descending pathways from these centers are likewise known (Lloyd,[16] 1941; McCulloch, Graf, and Magoun,[24] 1946; Niemer and Magoun,[25] 1947; Thulin,[28] 1953). Less information is available, however, concerning the site and mode of action of the reticular formation on spinal reflex pathways.

The purpose of the experiments to be reported here was that of studying the mode of the facilitatory action of the suprabulbar reticular formation upon elements of the monosynaptic and polysynaptic reflex arcs. A comparison was also made between the effects of reticular formation stimulation and the action of other pathways which were employed to produce facilitation of spinal reflex action. Inhibitory effects resulting from excitation of the suprabulbar formation were also studied, but these observations will be dealt with in another publication.

METHODS

Dial anesthesia (0.4 ml/kg.) with tubocurarine chloride (0.75 mg/kg.) was employed in a few preliminary experiments. In these instances stimulation of the reticular formation caused motoneuron discharges. It was decided to avoid such conditions, however, because of complications introduced by occlusion (Austin,[1] 1952) and by possible central excitatory action of curare (Chang,[6] 1953). A few experiments were also performed on animals decerebrated at a high level under ether and then maintained with only occasional recourse to this anesthetic, but for the most part cats lightly anesthetized with pentobarbital (Nembutal) (30-35 mg/kg.) were used in this study. Under conditions imposed by the latter techniques, stimulation of the reticular formation caused no discharge of motoneurons. In the experiments discussed here, therefore, only inhibitory and subthreshold excitatory actions resulting from stimulation of the suprabulbar reticular formation were studied.

A Horsley-Clarke stereotaxic instrument was used in making placement of the concentric and other bipolar electrodes employed for brain stimulation. Standard procedure was to stimulate centrally with 1-msec. square wave pulses at 100 to 200 per second for 15 seconds at a strength of 0.5 to 1.5 volts. Strengths of 3 to 5 volts were used on occasion. Reflex responses from muscle, skin, and mixed nerves were determined before, during, and after reticular formation and pyramidal tract stimulations.

The customary procedures (Brooks, Koizumi, and Malcolm [5]) were followed in exposure of the cord

Visiting Professor from the Department of Neurology, Brussels University Hospital (Dr. Kleyntjens).

From the Department of Physiology, State University of New York College of Medicine at New York City, Brooklyn.

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* References 16 and 18.

† References 21 and 22.

and preparation of peripheral nerves and spinal roots for stimulation and the recording of activity. All ventral roots below L4 were cut bilaterally to prevent any possible movement and reverberation of stimulation effects from peripheral receptors during and following central stimulation (Granit,[8] 1950; Lloyd,[17] 1941). The cord and peripheral nerves were protected by pools of liquid petrolatum (mineral oil), and normal temperatures were maintained by radiant heat.

Reflex discharges recorded from the ventral roots of L6, L7, and S1, dorsal cord potentials, dorsal and ventral root electrotonic potentials, and the orthodromic and antidromic potentials picked up from motoneuron pools were recorded by means of apparatus incorporating a D. C. preamplifier, usually alternating current coupled to a Cossor oscilloscope. This A. C. coupling had a time constant of 1 second. A D. C. coupling was employed in measuring electrotonic potentials and in detecting potential gradients between motoneuron pools and the ventral roots during reticular formation facilitatory activity. Reflex activity was evoked by stimulation of extensor (quadriceps, gastrocnemius) and flexor (hamstring) muscle afferents, and a skin nerve (sural) and mixed nerves (peroneal, tibialis posterior, sciatic) and by stretch of muscles (gastrocnemius) imposed by means of an electromagnetic mechanical transducer activated synchronously with the oscilloscope sweep through one of two Grass stimulators. The duration of the rising phase of the imposed tension was of the order of 4 msec.; the strength and duration of the pull was 30-35 gm. for 10 msec. These Grass stimulators were also employed for nerve and brain stimulation.

The position of the electrodes and the sites of stimulation were determined histologically. Other details of methodology will be discussed in connection with the descriptions of results obtained.

RESULTS

Facilitatory Effects on Monosynaptic Reflex.—During stimulation of a facilitatory area in the reticular formation there was a marked increase (200% to 500%) in amplitude of the monosynaptic reflex spike (Kleyntjens, Koizumi, and Brooks,[13] 1954). This facilitation generally built up gradually to a maximum and occasionally then decreased slightly before the end of the 15-second period of stimulation (Fig. 1*A*). It can be seen from this same Figure that immediately on termination of stimulation there was a sharp decrease of the spike height for

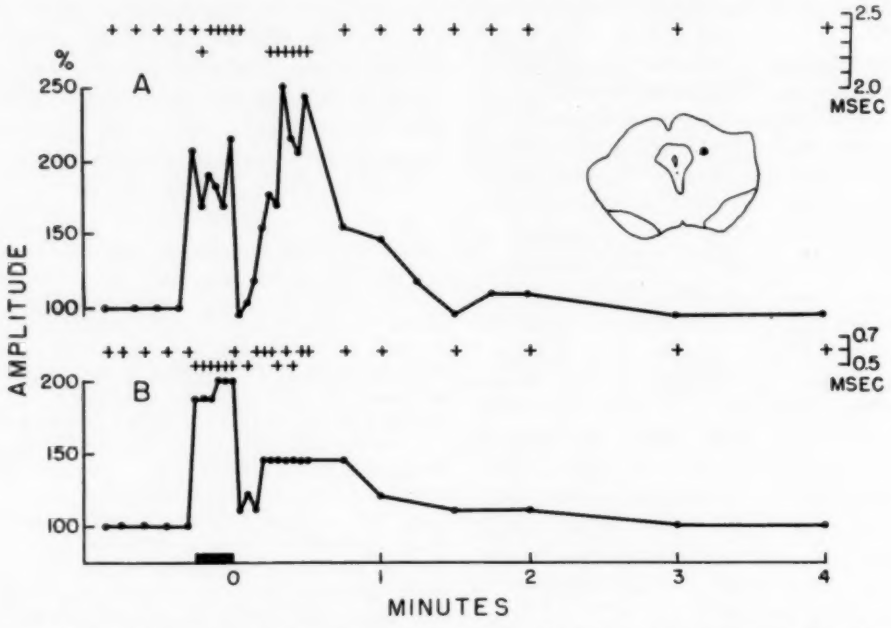

Fig. 1.—Effect of stimulating reticular formation for 15 seconds on (*A*) monosynaptic reflex induced by stimulation of afferents from gastrocnemius, (*B*) antidromic potential from seventh lumbar segment. Amplitude expressed in per cent of control spike height; time, in minutes after the end of reticular formation stimulation. Plus signs (+++) indicate latency of the response.

a period of 5 to 15 seconds. This, in turn, was succeeded by a long period of augmented response, which attained its peak at approximately 30-45 seconds after stimulation but persisted for 2 to 3 minutes, and rarely for 4½ and 5 minutes. The pattern of facilitation varied somewhat (Fig. 2*A*) but uniformly possessed these three phases: (1) a facilitation during stimulation, (2) a brief period of rebound or reduced facilitation immediately following stimulation, and (3) a subsequent long-lasting period of augmented response.

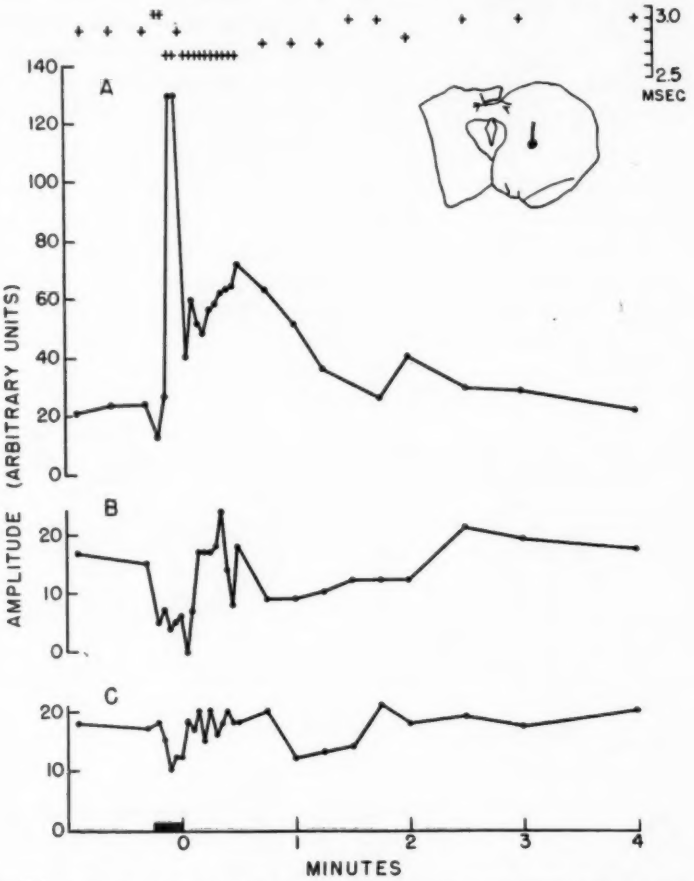

Fig. 2.—Effect of stimulating reticular formation on reflex response induced by stimulation of a mixed nerve (sciatic nerve). (+++), latency of monosynaptic response. *A*, change in monosynaptic component during and after the stimulation of reticular formation for 15 seconds. *B*, change in amplitude of polysynaptic component of reflex response. *C*, effect on amplitude of dorsal root reflex obtained from a root (L_6DR) adjacent to the root of afferent impulse entry (L_7DR).

This sequence of events occurred in the case of flexor as well as extensor afferent nerve stimulation, and when muscle afferents were activated by stretch. Stimulation of the suprabulbar reticular formation of either the homolateral or the contralateral side produced the same result. This work confirms the observation of others that the reticular formation has a bilateral (Lindsley, Schreiner, and Magoun,[15] 1949; Lloyd,[16] 1941; Neimer and Magoun,[25] 1947) and a diffuse rather than a selective action (Austin,[1] 1952; Bach,[2] 1950; Sprague and associates,[27] 1948; Thulin,[28] 1953).

Associated with the facilitation was a decrease in latency of the motoneuron response, as is shown in Figures 1 and 2. The shorten-

ing of latency varied in degree but generally amounted to 0.30 msec. The maximum decreases in latency coincided in the majority of cases with the maximal facilitation which occurred during the period of reticular formation stimulation. There was a prolongation of latency immediately after the stimulation during the phase of temporarily reduced facilitation; the latencies returned to normal or increased by 0.1 msec. above normal. During late facilitation latency again shortened by 0.25 to 0.3 msec. It appears, therefore, that stimulation of the reticular formation produces an excitatory background favorable to quick firing of the motoneurons by peripheral stimuli. The changes in latency tend to mirror the course of facilitation but are not always proportional to facilitation. More will be said concerning this matter in the discussion of antidromic and orthodromic focal potentials.

Another characteristic finding (Ingram and associates,[11] 1932) was an oscillation in the amplitudes of reflex discharges which was initiated by stimulation of the reticular formation. This fluctuation in spike height often began during stimulation but generally became more apparent during the phase of secondary facilitation, and it frequently lasted much longer than did the facilitation itself. Oscillation was occasionally evoked during experiments in which, owing to various circumstances, stimulation of the reticular formation gave only weak and short-lasting potentiation of reflex action. An exact determination of the rate of this rhythm was not made, but the testing stimuli given every second or every three seconds indicated that the rhythm was quite irregular; it was usually superimposed on the facilitatory curve, and it showed a progressive slowing. This result was similar to that obtained by Jenkner and Ward[12] (1953).

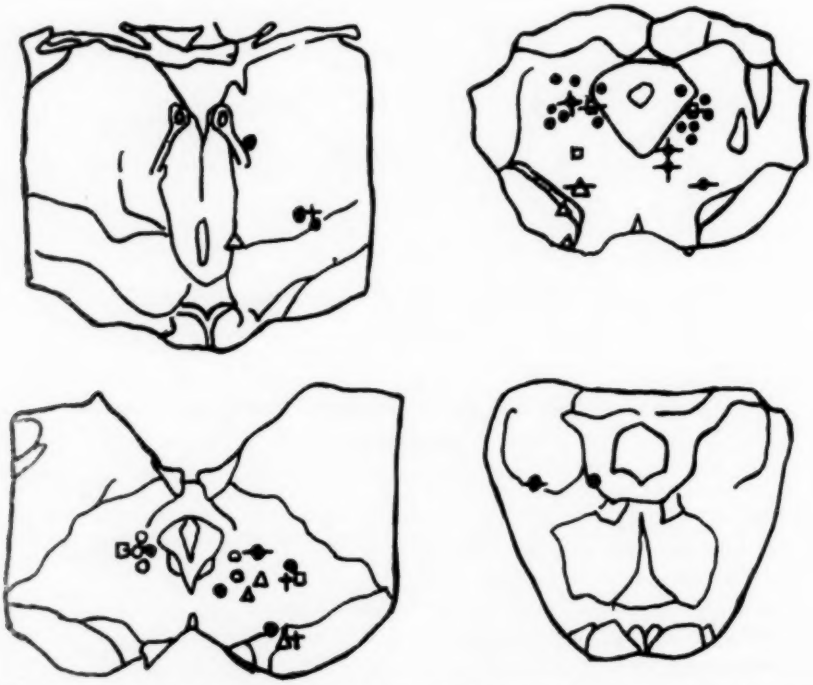

Fig. 3.—Location of points stimulated in the reticular formation to affect (1) monosynaptic reflexes, showing results obtained:

● facilitation during and after stimulation
△ facilitation during stimulation only
○ inhibition
□ mixture of facilitation and inhibition

(2) polysynaptic reflexes:
+ facilitation
— inhibition

The points from which immediate and long-lasting facilitation were obtained are shown in Figure 3. Facilitation during stimulation was more commonly obtained than the long-enduring after-effects, but it was concluded that this was due to conditions of the experiment, such as the depth of anesthesia, rather than to any selectivity of areas in the reticular formation. Variations in results of stimulation were due to conditions rather than electrode placement, because this was such that stimulation was confined to approximately the same area of the reticular formation.

Recording of the focal potentials created in motoneuron pools by orthodromic impulses from muscle afferents (Brooks and Eccles,[4] 1947) provided another means of studying the effects of reticular formation stimulation on the monosynaptic reflex pathway. It was found that excitation time, as indicated by the interval between the peak of the initial

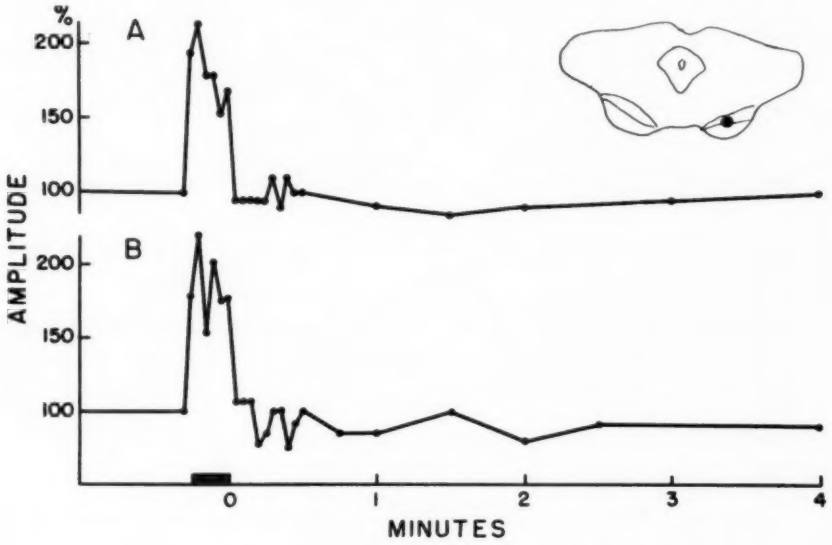

Fig. 4.—Effects of stimulation of pyramidal tract on the monosynaptic reflex (*A*) (stimulation of afferents from gastrocnemius muscle) and the antidromic potential picked up from seventh lumbar segment following stimulation of L_7VR (*B*). Amplitude expressed in per cent of control spike height.

Effects obtained by reticular formation stimulation were compared on numerous occasions with those resulting from similar stimulation of the pyramidal tract. Tetanic excitation of pyramidal fibers in the suprabulbar region did cause a facilitation of the monosynaptic reflex (Lloyd,[17] 1941), which was indistinguishable from that produced by reticular formation during stimulation, but a comparable late effect was never seen (Fig. 4*A*). Despite the evidence that the pyramidal fibers act on the motoneuron pool through terminal interneurons (Lloyd,[17] 1941) in somewhat the same fashion as do certain of the pathways from the reticular formation (Lloyd,[16] 1941), there was less of an after-effect from stimulation of the pyramids.

negative deflection of the potential and the origin of the propagated spike (Brooks, Koizumi, and Malcolm[5]) was shortened during periods of facilitation. This accounts in part for the decrease in latency. It is reasonable to conclude that discharges from the reticular formation so act upon afferent terminals and/or motoneurons that afferent impulses from the periphery can more quickly invade the individual efferent elements and can involve a higher percentage of the units of the motoneuron pools.

Changes in the frequency of stimulation between 60 and 300 per second did not modify the results from one and the same point. Changes in voltage of the stimulation, however, did modify the effects, and strong stimuli tended to produce inhibition.

Effects on Polysynaptic Reflexes.—Stimulation of points in the suprabulbar reticular formation which gave marked facilitation of the monosynaptic reflex produced only inhibition of the pure polysynaptic reflex in magnitude, persisted for two and a half to three minutes.

When mixed nerves were stimulated, a facilitation of the polysynaptic component of the reflex was occasionally obtained. This was greatest during stimulation, but the late phase of facilitation and the intermediate decrease were also seen (Fig. 6). In about half the experiments, although a very definite and typical facilitation of the monosynaptic component occurred, there was actually an

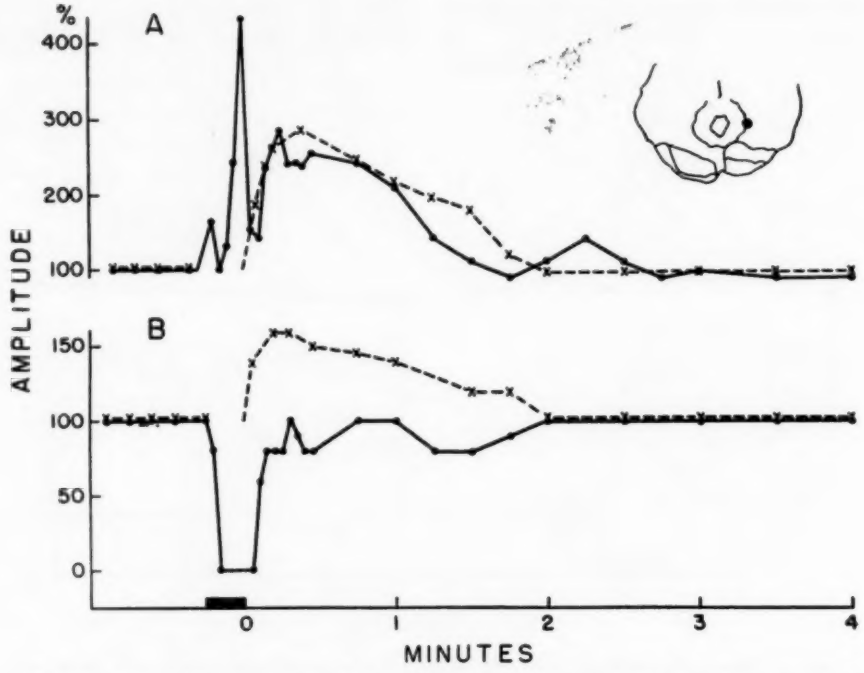

Fig. 5.—Comparison of post-tetanic potentiation (line of crosses) and the effects of reticular formation stimulation (line of dots) on (*A*) the monosynaptic reflex induced by stimulation of afferents from gastrocnemius and (*B*) the polysynaptic reflex elicited by stimulation of a sural nerve. Amplitude expressed in per cent of control spike height.

evoked by skin nerves (Fig. 5*B*). Although in six experiments numerous points in this region of the reticular formation were stimulated, no point was found which would facilitate a sural nerve reflex. After stimulation a reversal or a slight rebound occasionally was seen which persisted for 30 to 40 seconds, but nothing resembling the late facilitation of the monosynaptic reflex was produced. There was, on the contrary, a late phase of inhibition, which, though slight inhibition of the polysynaptic element of the reflex (Fig. 2*B*). These facilitatory and inhibitory effects were not related to the mixed nerve stimulated but were occasioned either by conditions of the preparation or by the points in the reticular area stimulated. Both effects were never evoked from the same point. In this series of experiments a facilitation of the polysynaptic element of the mixed nerve reflex was never obtained in the absence of facilitation of the monosynaptic component.

Effect on the Dorsal Root Reflex and Cord Potentials.—Dorsal root reflexes elicited by stretch of muscles or by stimulation of muscle nerves are minimal at normal cord temperature (Brooks, Koizumi, and Malcolm [8]). Stimulation of mixed nerves and skin nerves, however, does produce in roots adjacent to the root of impulse entry a definite dorsal root reflex of sufficient magnitude and stability to permit study. It has been reported previously (Hagbarth and Kerr,[10] 1954; Kleyntjens, Koizumi, and Brooks,[13] 1954) that stimulation of the reticular formation produces a diminution of this reflex. In early experiments changes in the dorsal root reflex occurred which were interpreted to be an augmentation, but these may have been artifactual; certainly no marked facilitation was observed. It can be said that the dorsal root reflex is generally suppressed.

In a few experiments potentials were recorded from the dorsal aspects of the cord. The secondary or intermediary components of these cord potentials were invariably reduced in magnitude during and for several seconds following reticular formation stimulation, as reported by Hagbarth and Kerr [10] (1954). The polysynaptic components of reflexes initiated by mixed nerve stimulation were never facilitated to as great a degree as were the monosynaptic reflexes by stimulation of the reticular formation, and inhibition occurred in many instances. Apparently, a mixture of inhibitory and facilitatory influences plays upon the elements of the polysynaptic pathway and the inhibitory effects tend to predominate. Presumably, the inhibited elements are interneurons.

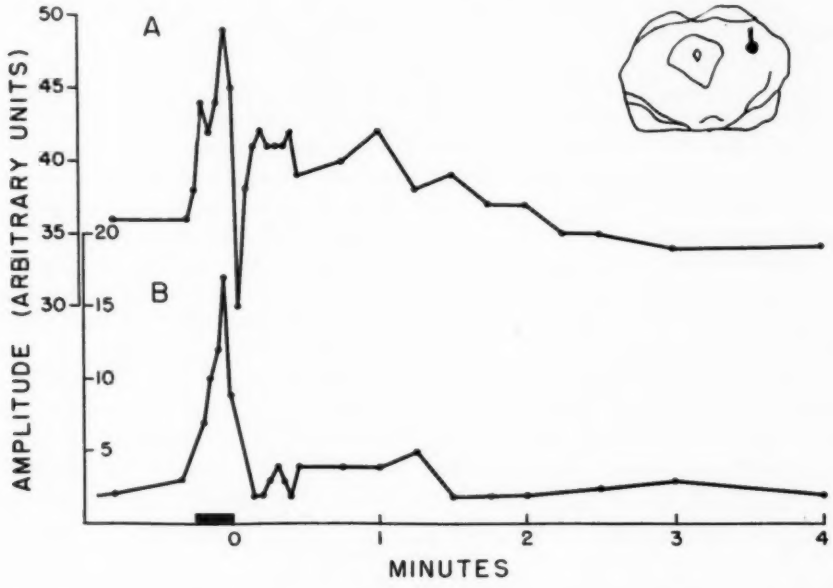

Fig. 6.—Facilitation of the monosynaptic component (*A*) and the polysynaptic component (*B*) of the reflex discharge induced in L_7VR by stimulation of sciatic nerve.

It has been claimed that the dorsal root reflex contains an element contributed by interneuron activity (Brooks and Kiozumi ‡; Lloyd and McIntyre,[20] 1949). This, theoretically, should augment or decrease with the changing balance of facilitation and inhibition in the interneuron pathway. Just why or how the dorsal root reflex could be inhibited

‡ Brooks, C. McC., and Koizumi, K.: Origin of the Dorsal Root Reflex, J. Neurophysiol., to be published.

when the polysynaptic reflex showed facilitation is difficult to explain. Two explanations are theoretically possible. First, it is conceivable that during facilitation from higher centers there might be a more generalized activity in the interneurons which would tend to mask or prevent a synchronized dorsal root discharge. In such case total interneuronal activity might actually be greater, although appearing to be less, owing to a more continuous and dispersed discharge out individual dorsal root elements. Second, it is possible that the direct action (Lloyd,[16] 1941) of the reticulospinal pathways on the motoneurons is sufficient in some cases to more than compensate for an inhibitory effect on interneurons. The fewer late or polysynaptic discharges which do get through the inhibited interneuronal pools actually are able to initiate a greater discharge than occurred normally.

This observed inhibition of the dorsal root reflex and of the secondary elements in the cord potential indicates that the facilitatory action of the reticular formation is not on interneurons or on the terminals of afferent fibers, since they contribute to the dorsal root potential (Lloyd and McIntyre,[20] 1949). Since the initial spike of the cord potential is uninhibited by reticular formation discharge (Hagbarth and Kerr,[10] 1954), this inhibition also does not act on the primary afferent fiber.

Effects on Antidromic Potentials.—More information concerning the site of action of the facilitatory impulses from the reticular formation was obtained by a study of antidromic potentials produced by ventral root stimulation and picked up from the ventrolateral surface of the cord or from within the motoneuron pool by focal recording. The antidromic potentials studied were those most facilitated by the orthodromic inpulses from the muscle nerve evoking the reflex under study.

It was found that stimulation of the reticular formation caused an augmentation in antidromic spike height and a reduction in its latency. The three phases of facilitatory effect were seen, as in the case of reflex facilitation (Fig. 1*B*). There was a doubling or tripling of spike height during stimulation, but the late phase of facilitation was of much smaller magnitude, and, owing possibly to the smaller amplitude of the spike, facilitation did not appear to persist for as long a time as did the augmentation of the reflex spike.

Simultaneous testing of two motoneuron pools showed that facilitation was usually much greater in one pool than in another, but this might have been due to a more favorable afferent-efferent ratio in one case or to a more favorable placement of the microelectrode in the pool.

In Figure 7 it can be seen that a facilitation of the antidromic potentials and monosynaptic spike occurred at a time when the dorsal cord potential and polysynaptic components of a mixed nerve reflex were inhibited. It can be observed in this case, as well as in Figure 1*B*, that there was a residual facilitation in the motoneuron pool which conceivably could have facilitated a late discharge provided impulses had reached the pool by way of interneurons or from the periphery.

One of the most interesting results obtained was a facilitation of the antidromic potential by a reticular formation stimulation which inhibited the monosynaptic reflex mediated by the same cord segment. The implications of this are such that the matter requires further investigation before conclusions can be drawn concerning this particular observation.

Facilitation from the Reticular Formation and Post-Tetanic Potentiation.—It was observed that the development and duration of the late facilitation of segmental reflexes resembled the post-tetanic potentiation produced by stimulation of afferent nerves (Lloyd,[19] 1949; Eccles and Rall,[7] 1951). These two phenomena were therefore compared in a series of animals.

Figure 5 shows facilitation of a reflex elicited from the afferent fibers of the gastrocnemius muscle by reticular formation stimulation and the post-tetanic potentiation produced by tetanization of these same

muscle afferents. A higher rate of peripheral tetanization was sometimes required to produce effects of the same magnitude as those elicited by reticular formation stimulation, but it can be seen that these late effects have a surprisingly similar amplitude and time course.

When these two phenomena were elicited together, by simultaneous tetanization of a peripheral nerve and the reticular formation, they did summate in some instances and in others at least had an additive action (Fig. 8). The two facilitatory processes can evidently supplement each other to such a degree that a higher percentage of the motoneurons of extensor and/or flexor muscle pools are brought into action by a single afferent volley. It was rather interesting to observe in certain cases that, as shown in Figure 9, a reticular formation stimulation which had a predominantly inhibitory effect on the monosynaptic reflex did nevertheless summate with a simultaneously applied peripheral nerve tetanus to give post-tetanic monosynaptic spikes which were greater in magnitude than those obtained after peripheral nerve tetanization alone. It appears that the long-lasting effects of the peripheral nerve tetanus are not prevented by inhibitory influences emanating from the reticular formation capable of blocking that reflex pathway.

This summation can be explained on the basis of the supposition that facilitatory forces are acting but are masked by the inhibition. The reticular formation stimulations which inhibit the monosynaptic reflex may have a facilitatory action on the motoneurons, as indicated by an increase in antidromic potential. The presynaptic action of peripheral nerve tetanization could summate with the postsynaptic effects of reticular formation stimulation. It becomes difficult, however, to explain where and how reticular formation inhibition acts in such cases. Presumably, when reticular formation stimulation inhibits both the reflex and the antidromic potentials the post-tetanic potentiation would be opposed, but more work must be done before

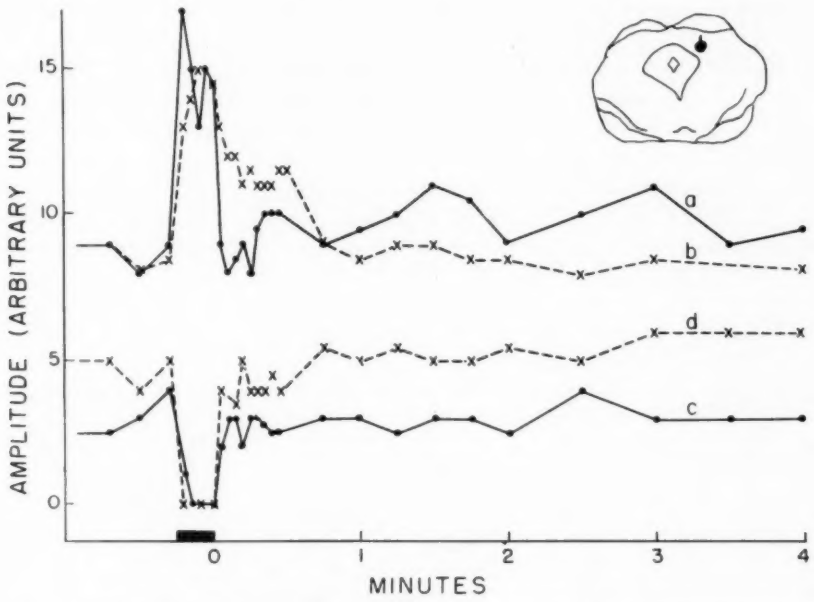

Fig. 7.—Effects of stimulating a point in the reticular formation on the monosynaptic reflex component (*a*), the antidromic potential induced in the seventh lumbar segment by stimulation of L_7VR (*b*), the polysynaptic reflex (*c*), and the intermediary cord potential (*d*). The sciatic was the afferent nerve stimulated to produce cord potentials and reflex discharges.

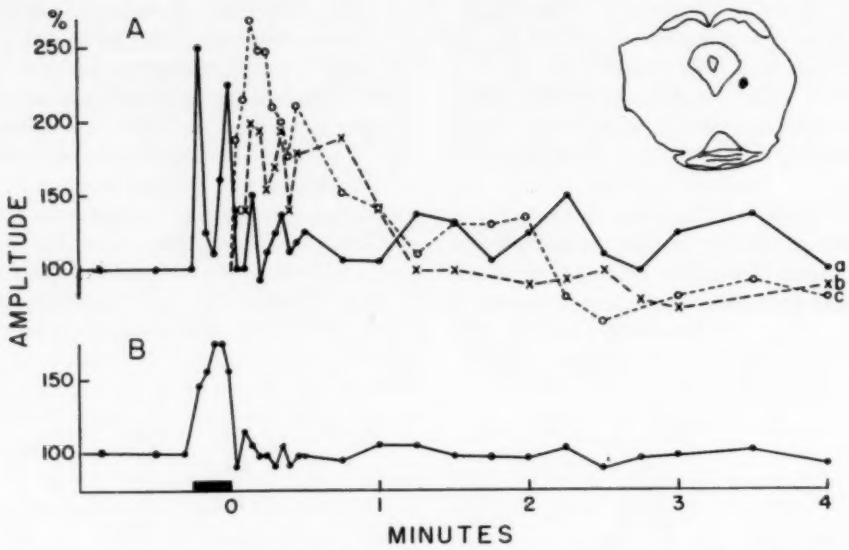

Fig. 8.—*A*, comparison of the effects of reticular formation stimulation alone (*a*), tetanic stimulation of the afferent nerve (*b*), and of the two stimuli given simultaneously (*c*) on the monosynaptic reflex induced by stimulation of afferents from the gastrocnemius muscle.

B, effects of stimulating the same point in the reticular formation on the antidromic potential. Change expressed in per cent of control spike height.

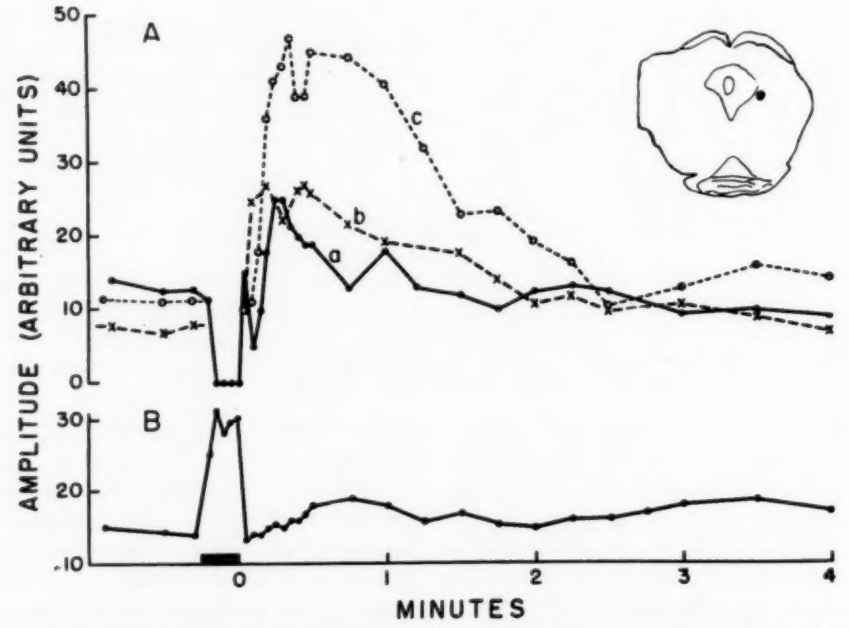

Fig. 9.—*A*, post-tetanic potentiation of a reflex induced by stimulation of afferents from gastrocnemius (*b*); effect on this same reflex produced by stimulation of reticular formation for 15 seconds (*a*); effect on the reflex of simultaneous reticular formation stimulation and afferent nerve tetanus (*c*).

B, change in antidromic potential produced by stimulation of the same point in reticular formation which inhibited the monosynaptic reflex during stimulation but had an after-effect which summated with peripheral nerve post-tetanic potentiation.

these observations can be explained and the problems presented by these mixed actions can be resolved.

Origin of Long-Lasting Facilitation Induced by Stimulation of Reticular Formation.—The long-lasting facilitation induced by reticular formation stimulation could not be due entirely to reverberation from the cerebral cortex, from other cerebral structures, or from the cerebellum, because it could still be evoked, though reduced in amplitude and duration, after decerebellation, decerebration, and removal of structures rostral to the area stimulated.

There was a barely detectable increase in background activity in the cord during periods of facilitation. This was picked up by means of microelectrodes recording focally from the ventral horn in the vicinity of the motoneuron pools. Either the increased discharge to or activity in the motoneuron pools initiated by monosynaptic reflexes was counterbalanced by the diminution of activity in interneuronal elements (Hagbarth and Kerr,[10] 1954), or there was such an asynchrony that an increase could not be detected, or the technique of recording was not adequate. This test did not lend very strong support to the concept that late facilitation was maintained by continued action of extrasegmental influences on the motoneuron pool.

Recording by means of a direct-coupled amplifier between a ventral root electrode adjacent to the cord and one located peripherally on the same root showed a temporary imbalance indicative of a greater central negativity coincident with the facilitation occurring at the time of stimulation (Gualtierotti,[9] 1952). During the poststimulation period of facilitation occasionally a central negativity was also recorded, but conditions were such that a marked nonreversing drift in one direction or the other most commonly occurred. These methods, therefore, gave little information concerning the origin of facilitatory influences acting on the motoneurons, but they showed that conditions in the motoneuron pool were favorable to activation of the neurons by entering afferent impulses.

Microelectrodes placed in the caudal extremities of the facilitatory areas of the reticular formation and/or the dorsolateral reticular formation of the medulla gave evidence of an augmented frequency of discharge of neural elements during stimulations which produced facilitation of the spinal reflex, but throughout the period of prolonged late facilitation there was no evidence of a prolonged discharge. There are numerous reasons why these techniques might not have revealed a continuous action of the reticular formation following brief periods of stimulation; therefore, the negative evidence merely leaves the problem of the late long-lasting facilitation unsolved.

COMMENT

The facilitation of the monosynaptic reflex which occurs during reticular formation stimulation can be compared with any interaction between excitatory fibers converging upon a motoneuron pool. Subthreshold excitation from higher levels or segmental pathways will facilitate the action of other volleys reaching these motoneurons. The next two phases of the facilitation are more difficult to explain. Since mixed inhibitory and facilitatory effects are often obtained from stimulation of the reticular formation, it might be thought that the brief period of rebound or reduced facilitation following termination of central stimulation might be due to inhibition breaking through facilitation at this time. This interpretation cannot be accepted without further support, however, because inhibition due to reticular formation stimulation does not invariably last longer than facilitation. Moreover, studies of the inhibitory processes indicate that inhibitory effects of reticular formation stimulation tend to mirror the facilitatory ones, and at the end of the central tetanus they rebound toward facilitation or diminish markedly in effectiveness. In certain experiments in which, owing to the use of curare and very light anesthesia, motor nerve discharges occurred during stimulation of the reticular formation it might be concluded that fatigue or accumulated refractoriness could account for this momentary

depression, but in the majority of these experiments there was no motor discharge during brain stimulation. The most reasonable explanation therefore seems to be either that higher centers reduce their discharge of facilitatory impulses immediately on cessation of the stimulation or that an after-positivity tends to accumulate in the motoneuron pool, similar to that which has been reported to follow a succession of synaptic potentials (Brooks, Downman, and Eccles,[8] 1950). The long-lasting, late-developing period of facilitation cannot be explained by persistence of a local excitatory state in individual motoneurons because the duration of synaptic potentials and local subliminal excitatory states is only of the order of 15-20 msec. Since local interneuronal activity appears to be at least partially inhibited, it is unreasonable to assume that local reverberating circuits within the cord segment could be responsible. Reverberation from peripheral receptors was eliminated by ventral root transections. Little is left to explain this phenomenon other than a long-lasting chemical action or continued discharge from the reticular formation due to some reverberation or persisting excitatory process acting there. A study of antidromic and orthodromic focal potentials recorded from the ventral horn and the recording with a direct-coupled amplifier from the central and peripheral ends of the ventral root did give evidence of the presence of depolarizing influences during central stimulation but did not provide convincing indication of long-lasting afterdischarge.

The late facilitation produced by reticular formation stimulation, although it resembles the post-tetanic potentiation resulting from stimulation of peripheral nerve, can hardly be due to the same phenomenon. Post-tetanic potentiation occurs only in the fiber paths which have been tetanized. The reticular formation-induced facilitation occurs when motoneurons have not been excited sufficiently to cause a propagated impulse and also when they have been caused to fire by the central stimulation. The conditions essential to post-tetanic potentiation are built up only when reflex discharges have occurred during peripheral nerve stimulation. The reticular formation-induced facilitation is at least in part postsynaptic, since the antidromic potential is augmented, but post-tetanic potentiation is presynaptic (Eccles and Rall,[7] 1950; Lloyd,[19] 1949). Finally, the facilitatory effects from the reticular formation may be sustained by a continued discharge from higher centers, but the post-tetanic potentiation originates from and is sustained by changes which are supposedly not continuously augmented.

Summation between these two types of post-tetanic potentiation of reflex activity could well be due to cooperation between the presynaptic and the postsynaptic effects.

The bilateral and diffuse nature of the potentiating effects of reticular formation activity on all monosynaptic reflexes indicates a general facilitatory action of this central complex on spinal centers. This influence, however, does appear to show a rhythmic variation in intensity. This work provides additional evidence that excitation of the reticular formation produces long-lasting effects and that hyperactivity of this region gives origin to an excitatory action of such a nature that a rhythmic fluctuation in motoneuron discharges tends to result (Jenkner and Ward,[12] 1953). An oscillatory change of the central excitatory state in the spinal nuclei was revealed by testing the reflex responses during and after reticular formation stimulation. Oscillation suggests a reverberation or an inconsistency of excitatory influences rather than a constant central excitatory process, such as would be produced by accumulation of a chemical mediator.

Removal of the cerebellum and decerebration did not abolish the long-lasting facilitatory effects of reticular formation stimulation but caused a marked reduction in its duration and amplitude. The tendency of the potentiated spikes to vary in amplitude in an oscillatory fashion likewise persisted. Stimulation of the pyramid did not give a long-lasting facilitation. Therefore, this phenomenon of late long-lasting facilitation is due principally to excitation of the reticular formation but

may be contributed to by reverberation through cerebral and cerebellar pathways.

SUMMARY

Stimulation of the suprabulbar reticular formation produced a facilitation of flexor and extensor monosynaptic reflexes which was greatest during stimulation, which decreased markedly immediately after cessation of stimulation and then developed a late phase which persisted for two and a half to four and a half minutes.

The polysynaptic reflex evoked by stimulation of a skin nerve was inhibited, and the polysynaptic components of mixed-nerve-evoked reflexes were frequently inhibited by stimulation of points which caused facilitation of the monosynaptic reflex. In about 50% of the cases, however, the polysynaptic element of the mixed-nerve reflex was facilitated, but not to as great a degree as was the monosynaptic component.

Antidromic potentials obtained from the cord segment transmitting the testing reflex were facilitated by reticular formation stimulation.

Dorsal root reflexes and the intermediary element of the cord potential were suppressed by reticular formation stimulation which facilitated the monosynaptic reflex.

The late facilitation produced by stimulation of the reticular formation resembled in amplitude and duration the post-tetanic potentiation produced by stimulation of muscle afferents. These two types of facilitation summated when elicited simultaneously. The presynaptic effect of one (post-tetanic potentiation) conceivably summated with the postsynaptic effects of the other.

The decrease in latency of the monosynaptic reflex during the periods of facilitation produced by reticular formation stimulation was explainable by a decrease in excitation time, as shown by the orthodromic focal potential recorded from the motoneuron pool.

A production of oscillations or fluctuations in reflex spike height by reticular formation stimulation was observed, and its possible implication in relation to the problem of tremor was noted.

Stimulation of certain areas in the reticular formation produced a mixture of facilitatory and inhibitory effects, requiring more study.

Stimulation of the pyramid, unlike stimulation of the reticular formation, produced facilitation which lasted for only a brief interval after stimulation.

Recording potential difference between the central and the peripheral portion of a ventral root by means of a direct-coupled amplifier showed that depolarizing forces act upon the motoneuron pool during periods of facilitation.

Decerebration and decerebellation reduced the amplitude and duration of the late phase of facilitation following reticular formation stimulation.

It is possible that the late and prolonged phase of facilitation is due to prolonged discharge from the reticular formation. Conclusive evidence of this was not obtainable by the methods employed.

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Perseveration at Various Levels of Complexity, with Comments on Delirium

MAX LEVIN, M.D., New York

Perseveration is seen in many functions, ranging from the simplest to the most complex. It will be considered here in relation to three functions: (1) the relatively simple motor functions of grasp and posture; (2) a more complex function, speech, and (3) the most complex function of all, mentation. The three functions, though they vary in complexity, show a common pattern and are governed by common principles. A further object of this paper will be to consider some biological aspects of perseveration, as seen especially from the standpoint of delirium.

GRASP AND POSTURE

We can learn much about perseveration by considering the grasp and its relaxation. Is the relaxation of the grasp a merely passive act, wherein the innervation of the "grasp center" somehow just comes to a halt? Or is it an active deed? Observation of infants gives the answer. An infant is clutching a rattle when you dangle before his eyes a new toy that appeals to him. Wide-eyed with interest, he undertakes to lay the rattle down and reaches for the new toy, only to find to his mortification that the rattle is still held tight in his fist. This shows that the relaxation of the grasp is an active deed. The infant can grasp all right but has not yet learned to relax the grasp at will. The persistence of the grasp when it no longer serves the infant's purpose is the prototype of perseveration. The infant's grasp outstays its welcome from immaturity of those higher pathways that serve to keep the grasp in check. In adults, paralysis of these pathways releases the grasp from control and results in forced grasping.

The perseverative nature of forced grasping is emphasized by its frequent association with perseveration in other motor functions. The case about to be cited is of special value because the patient was young and well preserved and was therefore able to give a clear account of his trouble, unlike so many patients with forced grasping, who are old and deteriorated.

A mechanic, age 32, with meningovascular syphilis, became acutely ill with symptoms suggestive of a small vascular lesion in the right frontal lobe.

Perseveration of Grasp on the Left.—The patient said that his left hand did not relax its grasp automatically; it relaxed only on studied effort. Thus, "If I get hold of the bed sheet, this [left] hand wants to hold on; it don't want to let go." He could always let go but had to concentrate on it. "If I study a little bit to let go, I can let go. I say to myself, 'I got hold of this sheet—now I'll let go'; then I can let go."

Perseveration of Posture in Left Upper Limb.—This was a striking finding. It was demonstrated in the following manner. Sitting in a chair, the patient was asked to do the finger-to-finger test continually; i. e., with hands clenched except for the index fingers, he was asked to touch index to index repeatedly and in regular rhythm, stretching each arm all the way out to the side after each contact. He was told to keep on doing this until further orders. Then, a quarter of a minute later he was suddenly brought to a halt, the examiner saying, "That's enough; now shut your eyes tight— as tight as you can—and keep them shut, real tight." The command to keep the eyes shut tight was calculated to divert his attention from his upper limbs. He obeyed and halted the finger-to-finger exercise, whereupon the right hand promptly relaxed and went to rest on the right thigh, while the left hand, remaining clenched, lagged in midair some 10 or 15 seconds and then relaxed and came down to the

thigh in slow motion. A photograph made five seconds after the command to halt shows the right hand resting relaxed on the thigh, while the left hand, clenched except for the index, is still poised in midair at shoulder level.

SPEECH

Perseveration of speech is a commonplace in brain injury, aphasia, and paralysis agitans, and cases need not be cited. It may also occur in schizophrenic and manic-depressive states, as in the following cases.

A catatonic youth of 20 showed perseveration of speech. He was presented at a staff meeting, and during the five minutes he was there he moved only his head, the rest of his body being completely stationary. When asked how he felt, he replied, "I'm sick." (In what way?) "I don't know." A few minutes later he was asked, "A little while ago you said you're sick. What did you mean by that?" He replied by asking, "What'd I *mean* by that?" (Yes.) He repeated, "What'd I *mean* by that?" (Yes.) Again he repeated, "What'd I *mean* by that?" He repeated the question five times, without any variation in tone. He then remained mum, not answering the examiner's question. (Why did you repeat the question so many times?) "You *made* me say that." No further elucidation could be obtained.

A man in a depression at the Harrisburg State Hospital was often seen to move his lips silently. Thus one day he asked me, "Do you think they're going to put me over on Ward 8 [the disturbed ward]?" As soon as he said this, his lips continued to move; and when asked what words he was forming, he said, "Over on Ward 8." When asked why he "repeated" these words, he replied, "After I finish saying something, the words follow through and I repeat them to myself. I want to know if I said it right. I want to know that I get the right words to you." During the lip movements there was no phonation, but, as he said, "the words are in my mind." The phenomenon lasted several months, until he got well of his depression.

The next case deals not with speech but with something related to it. A man became hebephrenic in his 50's, and his family said that the first oddity appeared in his behavior at the church choir, where he had sung all his life: he got into the habit of holding his notes too long, to such a degree that he was kicked out of the choir.

PERSEVERATION OF IDEA AND IMAGE

The principles considered thus far in relation to simpler functions apply also to the most complex function of all, mentation. Disease will cause an idea or an image to persist beyond its proper time.

Cerebral concussion will be considered first. The first two cases are my own.

A young woman driving her car to New York skidded on the wet road. The car turned all the way around, and the next thing she knew, she was lying on the grass beside the road. Since she remembered nothing of the passage from car to grass, we may infer a brief concussion. While she was lying on the grass, as she said later, "I couldn't get the conviction out of my mind, 'I'm still in the car on my way to New York.'"

Normally ideas remain active until inactivated by circumstance. When you are driving to New York, you have in your mind the idea that you are in your car en route to New York. You will not be conscious of this idea at every moment, for you will be thinking of many things as you drive; but the idea will be in the background if not the forefront of consciousness. Should you stop at a restaurant and get out of the car, the idea that you are in the car will go into temporary abeyance, since it no longer applies. The young woman's concussion prevented this suppression, and the idea persisted after it had ceased to apply.

A farmer riding his mule was struck by a truck; he was thrown into the air and landed on his head. He was unconscious a short while and then for several hours felt "bewildered, like in a dream." The mule was dead. During the bewildered state "I knew the mule was dead—they told me that—but I couldn't get it into my head that the mule *was* dead."

Forbes Winslow [1] reported the case of a girl of 6 years who while tossing playthings back and forth with her playmates was struck by an object and was knocked unconscious. After lying unconscious for 10 hours, she began to come to, whereupon she "immediately jumped to the margin of her bed, exclaiming, 'Where is it? Where did you throw it?' and immediately commenced throwing little articles from her dress, exclaiming, 'Catch these!' By these acts, she was manifestly continuing those physical operations and train of thought which had been so suddenly arrested by her fall."

Wolff and Curran [2] in their study of delirium mentioned two cases of post-traumatic delirium from automobile accidents, during which the patients "elaborately relived the scene of the accident, attempting with great

exertion to extricate themselves from the imaginary wreckage with every show of vivid fear."

Perseveration of idea may last anywhere from a few minutes to many decades. Hughlings Jackson [3] mentioned a case reported by Conolly:

> A young clergyman, when on the point of being married, suffered an injury of the head by which his understanding was entirely and permanently deranged. He lived in this condition until the age of eighty, and to the last talked of nothing but his approaching wedding.

It is clear from these examples that cerebral trauma can so disrupt cerebration as to interfere with the processes whereby an idea, when it is no longer valid or pertinent, is "dismissed from the mind." Perseveration of idea after trauma is comparable to that of speech after a sudden cerebral insult. Jackson often pointed out that the "recurring utterance" seen in some cases of aphasia represents the words the patient was saying, or was about to say, at the moment he was stricken.

Perseveration is seen after toxic damage, too. A man about to take a bath became unconscious from the action of an unvented gas heater. He was revived by methylene blue, and as he turned pink in color he screamed, "Turn off the gas!" When he was fully restored, he remembered preparing to take his bath, but nothing afterward.[4]

Another toxic case, one that I studied most carefully, occurred during an attack of "grippe" that my son had when he was almost 8 years old. For one day he was prostrated with high fever. At the end of the day he told my wife, "What made me uncomfortable today was that I didn't know what I was doing . . . . When I was sitting up, I didn't know whether I was sitting up or lying down. I had to pinch myself" (quotation not exact). Next day, speaking of the day before, he said, "I was lying down reading for a very long time. Then when I sat up, I felt like I was still lying down" (exact words). In this perseveration of body image I recognized the approach of delirium, a menace that came no closer.

FLEXIBILITY: PERSEVERATION AS THE HALLMARK OF DELIRIUM

Perseveration means the persistence of activity when it is no longer useful, and so it betrays a want of flexibility, of adaptability to changing circumstance. A prize fighter in the ring must be flexible, and if he is so numbed by injury that he can't duck in time he is licked. A general must be flexible; he must be able to alter his battle plans to meet a change in the tactical situation.

From this standpoint delirium is of special interest, for in this condition, to a degree found in none other excepting coma, flexibility is wanting. The disorientation of delirium is not haphazard. It bears a characteristic stamp: The delirious man has trouble grasping the unfamiliar and tends to mistake it for the familiar. Thus in hospital he is apt to think he is at home, and the nurse he will mistake for his wife.* It was Hughlings Jackson who recognized this tendency in delirium to mistake unfamiliar for familiar, and showed that it is no accident but is determined by the laws of cerebral physiology. It is remarkable that Jackson, who modestly disclaimed any knowledge of psychiatry, should have observed and understood a phenomenon that escaped the notice of a great psychiatrist like Kraepelin.

Inability to grasp the novel and unfamiliar is seen in the case of a farmer in hospital with delirium tremens. Hearing the scratchy sounds of an ancient phonograph at the other end of the ward, he mistook them for the crowing of a rooster. He saw something familiar in what was relatively unfamiliar.

Jackson [7] referred to the case of "a sack dealer [who] was delirious during erysipelas. The house-surgeon opened a small abscess in one eyelid while the patient was in a strait jacket. The patient's account of these circumstances was that he had been to a public house, that the landlord fastened him down with two sacks, and then poked out one eye."

This man in his delirium misinterpreted the novel experience of having an abscess

* References 5 and 6.

lanced by a surgeon. A man who probably was no stranger to the pubs in his neighborhood, he grasped the event in terms of a barroom brawl.

Weisenburg [8] reported the case of a man with a brain tumor who was delirious. Weisenburg noted: "When he was first examined by me he thought he was coming to have a hat fitted." Here, again, is the mistaking of unfamiliar for familiar. It's hard to grasp the idea that you are with a nerve doctor having your head examined. It's easier to grasp the idea that your head is being measured for a hat.

Flexibility is by no means wanting only in delirium. No man is completely flexible. We all tend to appreciate a stimulus in terms of previous experience. There is a lot of neurophysiology in the story of the small boy who thought that the Lord's Prayer begins with the words: "Our Father who art in heaven, *Harold* be Thy name." But, as I have said, it is in delirium that flexibility drops to its lowest point.

Fully to appreciate the disorientational pattern of delirium with its tendency to mistake unfamiliar for familiar, we must consider the contrasting pattern seen in schizophrenia. Schizophrenics too may be disoriented. Thus a schizophrenic may develop a bromide or alcoholic or other toxic delirium. And even if there is no toxemia, he may become disoriented through involvement of place, person, and time in his paranoid distortions. When a schizophrenic is disoriented, he behaves differently from the man who is not schizophrenic. Instead of seeing himself in familiar scenes, he tends to think in terms of the remote, the exotic, the bizarre. Thus I have seen schizophrenics at the Harrisburg State Hospital who, despite the fact that they had never been out of the State, identified the place as China, Japan, Ethiopia, and the like. A schizophrenic in a bromide delirium named the place as "China or Japan." On recovery from the delirium he remembered this statement and explained that he had got the idea from seeing an attendant putting shoes on another patient who made a wry face, as if the shoes were tight; the tight shoes made him think it was China. (This was in 1936, when China was less in our thoughts than today.) A delirious man who is not schizophrenic would be unlikely to have such an outlandish train of thought. Countless delirious patients have mistaken me for a son or brother or some other familiar person, but it was a schizophrenic who (in an alcoholic delirium) mistook me for Chancellor Dollfuss (in 1934, when Dollfuss was in the news).

There is, I submit, no difference in essence between the delirious man in hospital who thinks he is at home and the man who after a cerebral concussion persists in ideas once valid but valid no longer. The laws of perseveration apply to both.

PERSEVERATION IN HEALTHY PEOPLE

Thus far I have considered perseveration in cerebral disease. It occurs also in people who are perfectly well.

An aggressive Irishman from New York City told me the following story: On V-E Day he got word of the cease fire while stationed on a hillside at the front. A few minutes later he saw a German soldier coming down the hill across the way, hands up in surrender. He automatically raised his rifle and shot the German dead. He had fought all the way from Normandy and hated the enemy deeply. His feeling persisted after news of the cease fire.

There is the famous case of a baseball infielder who became an umpire when his playing days were over. Soon afterward he was working in the infield one day when a hot grounder came his way, and instinctively he scooped it up and tossed to first base. Deeply ingrained professional reflexes asserted themselves when they were no longer appropriate.

Persistence of habit cost a little girl her life. When Second Avenue in New York City became a one-way southbound highway, she was about to cross the Avenue from east to west. In stepping off the curb she looked to her left, as American children are trained

to do, and she was struck by a southbound car.

BRICKNER'S CASE

The evidence considered thus far would indicate that perseveration is a release phenomenon, a positive symptom due to paralysis of higher centers that are supposed to inhibit a movement or other function when that function no longer serves a useful purpose. I will now consider a case that might seem to contradict this view, a case reported by Brickner.[9] In an epileptic woman various areas in the cortex were electrically stimulated in the hope of finding a trigger zone. A small zone was found on the mesial aspect of Area 6 which on stimulation caused her to utter "syllables resembling 'err, err, err' in what seemed a stereotyped manner." The patient was then asked to recite the alphabet, during which the zone was sometimes stimulated for several seconds.

> Each time this was done, the letter being uttered at the moment of application of the stimulus was repeated. This repetition continued throughout the stimulation, ceasing instantly upon termination of the stimulus, when the ordinary saying of the alphabet was immediately resumed. . . . The phenomenon is exemplified in the following quotation from the patient. The italics represent the application of the stimulus. "ABCDEFG*HHHHHHH*IJKL M*NNNNNN*OPQ*RRRRR*STUVWXYZ." The performance could be repeated at will. . . . On questioning, she said that she was fully aware of what was occurring, but was unable to check herself.

This zone in Area 6 has something to do with speech, for Penfield has reported cases in which stimulation of the zone caused vocalization.

Does Brickner's case mean that there is a "center for perseveration," which on stimulation causes perseveration, in the same way that stimulation of a precentral motor area causes movement of a joint? Not at all (and I hasten to add that Brickner does not draw any such conclusion).

The effects of stimulation are not always positive. They may also be negative. The best example is the unconsciousness of an epileptic fit. Why is the patient unconscious during a fit? Since excitation reigns supreme and unchecked all over the cortex, one would think the patient would, if anything, be "hyperconscious." It is a paradox of human nature that the greatest paradoxes (like the greatest lies) are sometimes the hardest to recognize. It took a genius, Hughlings Jackson, to recognize that the unconsciousness of an epileptic fit is a paradox, and his explanation of it is a masterpiece of insight. Jackson said that the highest cerebral centers, the "organ of mind," cannot function when excitation is unbridled and lawless. The neural substrates of ideas and images are complex, and their useful function presupposes an orderly and harmonious sequence of excitations in various areas at various moments. He suggested an analogy. He said that if one might suppose a "locomotor center" in the brain, an epileptic discharge in that center would not cause the patient to run fast; on the contrary, it would bring locomotion to a halt, for locomotion demands a harmonious pattern of excitation in proper time and sequence.

There comes to mind the analogy of a legislative assembly, which does its work by means of orderly parliamentary procedure and decorum. The members speak one at a time. If everyone talked and shouted all at the same time, the result would be, not quicker and better action, but paralysis of action.

And so I submit that Brickner's case does not prove that the zone he stimulated contains a center for perseveration. Such a center is inconceivable. What the case shows is that there are pathways that inhibit movement (in this instance, speech); that these pathways pass through the zone that Brickner stimulated, and that this artificial stimulation disrupted the smooth functioning of the pathways, rendering them useless for the duration of the stimulus.

SUMMARY

Perseveration may occur at any level of brain function. Illustrations are given from the lower levels (the grasp, posture, and speech) and from the highest level of all (mentation). The fact that perseveration

may occur at levels so widely separate is in keeping with the principle that all levels of the nervous system, however they may differ in complexity, are fundamentally of the same constitution.[10]

Perseveration indicates a want of flexibility, an inability to modify behavior (including mentation) to meet a change in situation. This inability to react efficiently to changing circumstance is, in the sphere of mentation, most strikingly exemplified in delirium.

350 Central Park West (25).

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Validity of Rorschach Test as Measure of Psychological Effects of Brain Damage

RALPH M. REITAN, Ph.D., Indianapolis

For more than 15 years the Rorschach test has been cited as an advantageous technique for measurement of the psychological effects of brain damage.[1] In a recent review of investigations concerning this problem, Klebanoff and associates [1] said:

> It is unfortunate that most studies of personality changes in organic brain disease have utilized the Rorschach test and reliance upon test signs which have not been adequately cross validated.

Neither the reliability nor the validity of the indications of brain damage from the Rorschach test has been adequately studied. The purpose of the present study was (*a*) to investigate the validity of certain Rorschach indicators of brain damage and (*b*) to explore further the intellectual and affective changes characteristic of brain damage.

MATERIAL AND METHODS

Population.—Fifty patients with proved brain damage or dysfunction composed one group. A second group consisted of 50 persons who had received neurological examinations before testing and who showed no signs or symptoms of cerebral damage or dysfunction. Thorough histories relating to brain injuries and diseases were obtained from each patient. None of the control subjects had positive anamnestic findings. The groups were identical with those used in a previous investigation of the validity of Halstead's tests of biological intelligence.[2]

The subjects in the two groups were very closely matched in pairs on the basis of color, sex, chronological age, and years of formal education. Differences in central tendency and variability between the groups on the latter variables did not approach statistical significance. Thirty-five men and 15 women were included in each group.

Each patient was interviewed before testing, and only those were included in the study who were alert and able to provide detailed anamnestic information which agreed with that from outside sources. Although many of the brain-damaged patients were examined postoperatively, none were acutely ill at the time of testing. Postoperative testing was delayed until maximal benefits from hospitalization had been received and the patients were ready for discharge. The group was heterogeneous with respect to location, extent, and type of brain damage. A substantial proportion of paraplegic and neurotic patients were included in the group without brain damage as a conservative procedure to minimize the possibility that intergroup differences could be attributed to hospitalization, chronic illness, or affective disturbances.

Procedure.— The procedure, generally stated, was to compare the Rorschach records in the two groups to determine whether or not the test described any reliable differences. The Rorschach test was administered to each of the subjects individually and the scoring was completed (Beck's method [3]) before either of the groups was composed or the subjects matched on the controlled variables. Means and standard deviations for the quantitatively scored Rorschach variables were calculated. Intergroup statistical comparisons of the mean differences were made by use of the *t* technique, employing the method for correlated groups. Comparison of the frequency of occurrence of various "signs" of organically impaired cerebral functions was made by use of the chi-square test, using Yates' correction for continuity when the expected frequency in any cell was less than 10. Finally, the Rorschach records were reviewed individually in an effort to discover consistencies in interpretation that would differentiate or characterize the groups.

RESULTS

The Table presents means, standard deviations, *t* ratios, and probability levels for

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From the Department of Surgery, Section of Neurological Surgery, Indiana University School of Medicine.

the two groups on various Rorschach variables.

From inspection of the Table, it is apparent that the group without brain damage had the higher mean values on each variable except F–. This result is more easily observed in a graphic representation. Figure 1 portrays the mean values for the groups, each variable being placed on an equivalent scale. The equivalent scale for the Rorschach variables was constructed by combining the two groups and converting the raw scores for each variable into T scores. The ordinate in Figure 1 is, therefore, a T-score scale. The means for each group were plotted on the graph in accordance with their equivalent T scores. Although this procedure tends perhaps to depreciate the extent of the differences between the groups, in so far as the treatment assumes that they belong to a single population, it has a major advantage in permitting a visual evaluation of the trend in the differences.

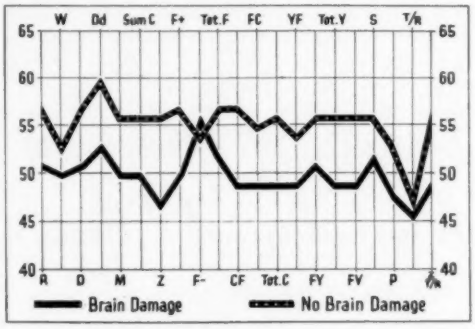

Fig. 1.—Graphic presentation of mean scores converted to T scores on Rorschach variables for equated groups with and without brain damage.

Distribution Constants, t Ratios, and Probability Levels for Equated Groups With and Without Brain Damage on Rorschach Variables

	R	W	D	Dd	M	Sum C	Z	F+	F–	Total F
No brain damage										
Mean	29.29	8.78	17.73	2.78	2.88	5.21	41.63	11.37	3.39	15.67
S. D.	20.81	5.00	15.68	6.54	4.00	3.99	23.27	8.66	3.86	13.20
Brain damage										
Mean	18.06	7.02	9.60	0.84	1.34	2.88	27.86	6.96	3.76	10.94
S. D.	10.60	3.82	8.24	1.55	1.60	2.61	15.08	5.23	4.09	8.05
t ratios	3.98	1.45	3.75	2.09	2.57	4.09	3.45	3.26	0.67	2.66
P <	0.001	ns	0.001	0.05	0.02	0.001	0.01	0.01	ns	0.02

	CF	FC	Total C	YF	FY	Total Y	FV	S	P	T/R	Z T/R
No brain damage											
Mean	3.43	2.20	5.90	0.8163	2.67	3.51	1.20	3.31	6.35	50.41	1.0461
S. D.	3.09	2.02	4.14	1.04	2.46	2.93	1.67	3.83	2.83	27.26	0.6721
Brain damage											
Mean	1.58	1.36	3.32	0.36	1.56	1.92	0.44	1.54	4.76	56.64	0.6722
S. D.	2.13	1.16	2.68	0.71	1.56	1.83	0.67	2.55	2.75	33.75	0.5183
t ratios	4.00	2.55	4.61	2.71	2.80	3.27	2.92	2.67	2.77	1.12	3.04
P <	0.001	0.02	0.001	0.01	0.01	0.01	0.01	0.02	0.01	ns	0.01

The intergroup differences shown in Figure 1 are obviously rather considerable, since 10 points on either side of the mean (a T score of 50) represents one standard deviation. A nearly complete lack of overlap argues strongly that there is a real difference in the diagnostic groups as measured by the quantitative Rorschach scores. The one reversal, F–, may also be considered in line with expectancy, since the brain-damaged group had the higher mean. With respect to T/R (time per response), expectation of a longer T/R for the brain-damaged group from previous studies * led us to reverse the distribution for purposes of the graph. Thus, while no reversal is shown on this variable, the brain-damaged group had the poorer score.

The fact that some of the Rorschach variables are interdependent measures introduces some difficulty in interpretation of Figure 1. For example, the number of whole responses (W) is limited by the total number of re-

* References 4 through 8.

sponses (R), and when (R) is higher in one group than in another, one would expect that (W) might also be higher. Dependency of this type makes a contribution of unknown value to the trend shown in the graph. However, a number of variables are independent measures. The lack of reversals among these independent measures suggests that the graph portrays a trend that is more than a statistical artifact.

The Table also presents *t* ratios which indicate the probability that the obtained mean differences may be due to chance.

For 49 degrees of freedom, a *t* ratio greater than 3.46 is needed to reach the 0.001 confidence level, greater than 2.66 for the 0.01 level, greater than 2.39 for the 0.02 level, and greater than 2.00 for the 0.05 level.

The *t* ratios in the Table are significant beyond the 0.05 level in 18 of 21 instances. Of the 18 significant mean differences, 5 exceed the 0.001 level (R, D, Sum C, CF, Total C); 8, the 0.01 level (Z, F +, YF, FY, Total Y, FV, P, $\frac{Z}{T/R}$); 4, the 0.02 level (M, Total F, FC, S), and 1, the 0.05 level (Dd). The variables which failed to show significant differences were W, F–, and T/R.

Each of the significant mean differences was in the expected direction; i. e., the group with brain damage had the lower value. The consistency with which the differences reached significant levels suggests that brain damage causes a generalized suppression of personality factors. Variables supposedly relating primarily to either intellectual or affective functions were both significantly reduced.

As another approach to possible quantitative differentiation of the groups, the Rorschach records were studied with reference to the frequency of occurrence of various "signs" of impaired psychological functions due to organic brain damage. The 10 signs proposed by Piotrowski [9] and the 9 signs proposed by Aita, Reitan, and Ruth were evaluated. Previously reported evidence † has indicated that at least some of these signs are related to the organic condition of the brain. Although their psychological meaning has not been completely established or clearly differentiated, their significant relationship to Halstead's measures of biological intelligence ‡ suggests their potential value as psychological indicators.

Figure 2 indicates the comparative frequency of occurrence of Piotrowski's signs in the two groups.

The ordinate in this graph (Fig. 2) is a percentage scale. The percentage of subjects showing each of the signs is indicated. Although some of the signs show a relatively small percentage difference in the two groups, the pattern of findings is again consistent. In no instance did the brain-damaged group have a lower percentage of subjects showing signs than did the group without brain damage.

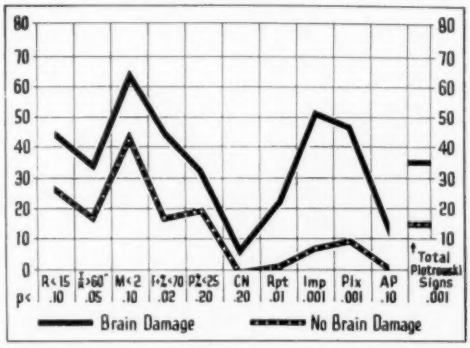

Fig. 2.—Comparative frequencies (shown in percentages of total groups) of patients with and without brain damage on Piotrowski's "signs" of organic brain damage.

A statistical evaluation of the comparative frequency of the signs was made with the chi-square test, using Yates' correction for continuity when expected frequencies were below 10. The probability of the intergroup frequency differences occurring by chance, shown in Figure 2, indicates the differential value of the signs. Impotence and Perplexity show significant differences beyond the 0.001 level. Repetition (*Rpt*) is significant beyond 0.01; *F+% <70* beyond 0.02, and *T/R*

† References 10 and 4 through 8.

‡ Reitan, R. M.: Relationships of Certain Rorschach Test Indicators to the Abstraction and Power Factors of Biological Intelligence, unpublished Ph.D. dissertation, University of Chicago, 1950.

>60" beyond 0.05. The remaining signs failed to show significant differences. Differences in the total frequency of Piotrowski's signs in the two groups were highly significant.

Figure 3 shows graphically the frequency of occurrence of the signs proposed by Aita, Reitan, and Ruth.

Two of these signs (*CR* and *Def*) are significant beyond the 0.001 level, and three additional signs *(Catas, Inflx, and W & R)*, beyond the 0.01 level. Again, the total frequency of signs differentiates the two groups at a highly significant level.

A review of the Rorschach records from an interpretative viewpoint was made in an effort to determine any outstanding features which might differentiate the groups. Al-

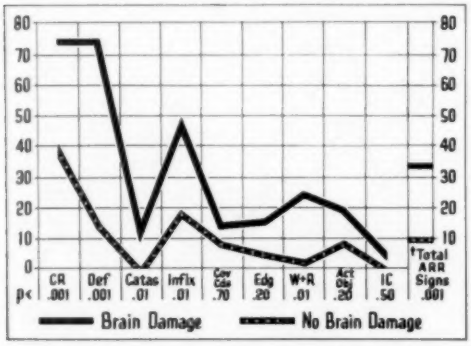

Fig. 3.—Comparative frequencies (shown in percentages of total groups) of patients with and without brain damage on the Aita-Reitan-Ruth "signs" of brain damage.

though indications of neurotic-like tendencies, including concern over bodily functions, depression, and hysteria, were present in the brain-damaged group, these indications also occurred frequently in the group without brain damage. This finding, undoubtedly, is an expression of our deliberate composition of the control group, including a large proportion of neurotic and paraplegic patients. Rorschach protocols of occasional patients in the brain-damaged group showed fairly severe deterioration of both intellectual and affective functions. Our impression from the subjective review of the records substantiates those reported in previous studies.§

§ References 5 through 8 and 10.

COMMENT

The results indicate that most of the quantitatively scored Rorschach variables, as well as a number of the "signs of brain damage," significantly differentiate between equated groups with and without brain damage. The fact that nearly all of the quantitatively scored variables were suppressed in the brain-damaged group suggests impairment of both intellectual and affective spontaneous expression, although evidence of neurotic-like disturbances is present. Signs of brain damage which occur with greater frequency at statistically significant levels included ones apparently related more closely to both intellectual and affective functions. The brain-damaged patients were slower in forming associations, tended to give less realistic associations, repeated responses without regard for form, often recognized the inadequacy of responses but were unable to improve or withdraw them, tended to give more concrete responses, were less able to define associations clearly, tended to withdraw from the problem and then reapproach it apparently in an effort to gain a new set, and were less able than the controls in giving more than one association to a single stimulus complex. In addition, however, signs occurred more frequently among the brain-damaged patients which seem rather clearly to relate to emotional reactions arising from the test. Brain-damaged patients more frequently seemed to distrust their ability and to seek help from the examiner, as well as to engage in overt catastrophic emotional reactions as their difficulty with the test situation mounted.

In spite of the statistical significance of the intergroup differences noted above, a very considerable overlap in the group distributions was present for both the quantitative variables and the signs of brain damage. The overlap is sufficient to make routine application of the results to individual patients difficult. Differences between groups with and without brain damage appear only to a matter of degree. The ability to identify reliably the indications of brain damage in an individual Rorschach protocol is dependent to a heavy extent upon very personal and

relatively incommunicable knowledge gained through extensive experience with individual patients. This situation represents a severe handicap in widespread use of the test for this purpose and almost certainly guarantees wide variance in the validity of conclusions from one examiner to another. Nevertheless, the results obtained in this and other studies suggest that the Rorschach method provides an avenue for the development of this type of personal knowledge and skill.

The advantage of tests of the psychological effects of brain damage which are strictly standardized and yield quantitative results which may be interpreted with a minimum of subjective evaluation is obvious. The same groups of patients were compared in a previous study [2] on Halstead's [11] tests of biological intelligence. The Halstead Impairment Index, as well as 8 of his 10 "discriminating" tests, yielded results which differentiated the groups at much more extreme confidence levels than were obtained with the Rorschach test. Not a single reversal between groups was present for the 50 pairs of patients on the Impairment Index, although for 6 pairs the results were equal. In only 3 of the 50 pairs did the brain-damaged patients perform better on the Halstead Category Test than did the matched controls. Since Halstead's tests are so strictly standardized that they may be administered by a technician, and in consideration of their nearly perfect differentiation of patients with and without brain damage, they are of considerably greater value than the Rorschach test. In addition, they provide a basis for reliable assessment of relatively mild psychological impairment associated with brain damage which might easily be missed with the Rorschach test. Since, however, Halstead's tests are relatively unavailable and the Rorschach test is in wide use, the significance of indications of brain damage on the latter test deserves careful study.

Comparison of the results in the present study with those obtained by Aita, Reitan, and Ruth [10] suggests certain differences. Aita and associates compared patients having post-traumatic brain injuries with hospitalized control patients, many of whom were neurotic. Their results indicated relatively little difference in the means of the quantitatively scored variables, whereas the present study shows significant differences on 18 of 21 of these variables. The frequency of signs of brain damage was somewhat greater in the study by Aita and associates than in the present findings. A recent investigation comparing groups of patients with penetrating head injuries and surgical cerebral excisions ‖ provides a tentative basis for relating these differences to the type of brain injury. This investigation used small groups, but the patients were individually matched for sex, color, chronological age, years of formal education, and intelligence quotient. The results indicated a trend for the patients with brain surgery to have lower quantitative Rorschach scores, but also to show fewer of the signs of brain damage. Since the brain-damaged patients in the present study were heterogenous with respect to type of injury, including patients with brain surgery, as well as those with closed and penetrating head injuries, the finding of somewhat lower quantitative scores and fewer signs of brain damage than those reported by Aita and co-workers [10] is consistent.

Results suggesting differences in Rorschach indications of brain damage depending upon the type of lesion suggest that attempts to validate previous studies using groups with differing types of brain damage may be in serious error. As an example, we can have no assurance that the criticism by Diers and Brown [12] of the Rorschach "signs" proposed by Hughes [13] is legitimate, since Diers and Brown studied patients with multiple sclerosis and Hughes based his signs on a group with heterogeneous types of brain damage.

The results of this study agree generally with those reported by Hertz and Loehrke [14] and substantiate their conclusion that while the Rorschach test may in some instances

‖ Reitan, R. M.: Comparative Psychological Findings in Patients with Surgical Cerebral Excisions and Penetrating Head Injuries, unpublished paper.

provide definite evidence of organic cerebral pathology, the absence of the customary indications in a Rorschach record does not necessarily contraindicate brain damage. In other words, the lack of specificity of Rorschach indications of brain damage requires that the criterion point be set so high, in order to exclude patients without brain damage, that a considerable proportion of false negatives occur.

SUMMARY AND CONCLUSIONS

In an experiment designed to investigate the validity of Rorschach test indications of brain damage and to explore further the intellectual and affective changes associated with brain damage, the Rorschach test was individually administered to 50 persons with proved brain damage or dysfunction and 50 matched controls with negative neurological and anamnestic findings. The subjects in the two groups were very closely matched in pairs on the basis of color, sex, chronological age, and years of formal education. In the brain-damaged group the cerebral lesions were heterogenous with respect to type, location, and extent. The control group included a substantial proportion of paraplegic and neurotic patients to minimize the possibility that intergroup differences might be attributed to hospitalization, chronic illness, and affective disorders.

The results indicated a thoroughgoing suppression of mean values for the brain-damaged group on quantitatively scored Rorschach variables. In 18 of 21 instances, statistical comparisons indicated that the means for the brain-damaged group were significantly lower than those for the controls. The consistency with which the differences reached statistically significant levels suggested that brain damage causes a generalized suppression of personality factors. Variables supposedly relating primarily to either intellectual or affective functions were significantly reduced. Evaluation of the frequency of occurrence of Rorschach test "signs" of brain damage indicated that they have some value in differentiating the groups. The brain-damaged patients tended to give less realistic associations, repeated responses without regard for form, often recognized the inadequacy of responses but were unable to improve or withdraw them, tended to give more concrete responses, were less able to define associations clearly, tended to withdraw from the problem and then reapproach it apparently in an effort to regain a new set, were less able in giving more than one association to a single stimulus complex, more frequently seemed to distrust their ability and sought help from the examiner, and sometimes engaged in overt catastrophic emotional reactions as their difficulty with the test situation mounted. The ability to identify reliably these indications of brain damage in an individual Rorschach protocol is dependent to a heavy extent upon the examiner's experience. In addition, it should be noted that differences in the occurrence of these signs between the group with and the group without brain damage seemed to appear only to a matter of degree. They do not constitute a basis for perfect discrimination even in the hands of an experienced examiner.

The same groups of patients were previously compared on Halstead's tests of biological intelligence. The Halstead Impairment Index, as well as 8 of his 10 "discriminating" tests, yielded results which differentiated the groups at much more extreme confidence levels than were obtained with the Rorschach test. In spite of the considerably closer approach to perfect differentiation of the patients according to diagnosis obtained with Halstead's tests, the availability and widespread use of the Rorschach test, together with the relatively encouraging results obtained, suggest the value of further investigation of the psychological effects of brain damage with this test.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Benjamin Boshes, M.D., *President*

Oscar Sugar, M.D., *Secretary*

Nov. 9, 1954

The regular meeting of the Chicago Neurological Society was held on Tuesday, Nov. 9, 1954, with the President, Dr. Benjamin Boshes, in the chair.

Infected Subdural Effusions. Dr. John Hankinson and Dr. Luis V. Amador (by invitation).

This condition has been more frequently encountered in recent years because of the improved chances of survival of children suffering from meningitis and because of the increased awareness of pediatricians of the possibility of subdural fluid collections. A case was described by Schwartz in 1916, but in 1945 Spitz and associates encountered only 2 cases in a series of postmortem examinations of 95 consecutive deaths from meningitis, in a total of 5000 autopsies. However, among other writers, Mackay (1953) and Smith (1951) and their associates found that approximately half their cases of meningitis in infancy were complicated by subdural effusion. This complication is particularly likely in meningitis due to Hemophilus influenzae, Pneumococcus, and Meningococcus. Five case histories are presented illustrating the clinical picture of this complication, and the methods of treatment are discussed. The indications for subdural tap are failure of clinical improvement after 24 hours' adequate therapy, persistent fever, convulsions or vomiting, and the presence of definite neurological defects. In particular, abnormal tension of the fontanelle or, at a later age, suture diastasis is an absolute indication for investigation of the subdural space. As with subdural hematomas, early tapping may be adequate, but craniotomy and removal of membranes may be necessary. One case presented had huge bilateral empyemas in the subdural spaces from which hematomas had been evacuated four years previously. Early intensive antibiotic therapy in meningitis is reemphasized, as also is frequent and careful observation of the neurological status, so that subdural effusions are recognized early.

Bilateral Glioblastoma Multiforme with Invasion of the Corpus Callosum, Clinically Simulating Chronic Encephalitis. Dr. Ernest Haase.

A 56-year-old physician, suffering from mild ambulatory "flu," suddenly developed left-sided Jacksonian convulsions and slight left hemiparesis, associated with temperatures up to 100 and 102 F. Virus study revealed influenza A virus. The hemiplegia subsided, and the convulsions were well controlled by anticonvulsants. Three months later a similar episode occurred, but with right-sided seizures. One year later there was rapid development of right hemiplegia with preservation of tonus, trophic functions, and reflexes, featuring a complete motionless or total apraxia. Mental deterioration followed, characterized by strange apathy, passive dependency, and complete loss of interest and purpose, alternating with episodes of severe agitation, frantic struggle for survival, and wild, animalistic outcries of deep anguish. After three months of downhill course, the patient went into coma and died. All the time no clinical signs of increased intracranial pressure could be observed: there were hardly any headaches, no papilledema, normal x-ray skull pictures, and a spinal fluid pressure of 150 mm. of water and not more than 65 mg/100 cc. of total protein. Repeated electroencephalographic records, with the patient awake and asleep, were normal.

At autopsy, the midportion of the corpus callosum was found to be the seat of a soft, dirty-gray tumor mass with a colloidal cyst in its lower portion. The tumor extended into the right supracallosal region, softening and macerating the cortex, and into the left hemisphere up to the occipital lobe, depressing the ventricular system and showing cystic degeneration in its lateral portion, bordering upon the centrum semiovale. The microscopic diagnosis was that of a glioblastoma multiforme.

DISCUSSION

DR. PERCIVAL BAILEY: I saw this man when his illness began, in consultation with Dr. Haase. At that time the patient had a hemiballismus on the left side and was quite mentally disturbed. I personally do not see how one can reconcile his symptoms with what was found in his brain after he died. There was nothing in the corpus Luysi to explain the hemiballismus that he had. I do not know how to explain the complete hemiplegia and the abnormal mental behavior and correlate them with the lesion. We have to fall back on the old term diaschisis, or something like that, because of the disturbances in the other parts of the nervous system.

Neurological Surgery in South America. DR. PAUL C. BUCY.

In the spring of 1954 Dr. Bucy spent three months in South America, having been invited to Brazil to serve as Visiting Professor at the Universidade de Minas Gerais, at Belo Horizonte. Several other countries were also visited. The outstanding medical features that impressed Dr. Bucy included the fact that infectious diseases which are susceptible of prevention form a large and important part of the diseases throughout South America. These include tuberculoma of the brain and tuberculous meningitis, which are prevalent almost everywhere but are problems of great importance in Peru and Chile. Cysticercosis of the brain is a common neurological disease in these countries and in Brazil. Leprosy is prevalent in Brazil also. Schistosomiasis and trypanosomiasis (Chagas' disease) are also common in Brazil, but rarely affect the nervous system. In Argentina and Uruguay the problem peculiar to these countries is hydatid cyst (Echinococcus cyst) of the brain, lungs, and liver. However, the principal medical problem in Argentina is the oppression of a political dictatorship which has no comprehension of the needs of medical education and research and which demands complete subservience from those doctors who would teach in the universities or conduct research in the laboratories. The leading neurosurgical institutions of South America are the Institute of Asenjo, in Santiago, Chile, and the Institute of of Neurology, under the direction of Dr. Roman Arana Iñiguez, in Montevideo, Uruguay. The latter is badly in need of a much more adequate physical plant. The medical schools of Brazil are very poor except for those of São Paulo and Rio de Janeiro. It is a country of great natural resources, which ultimately must and will be developed; but satisfactory progress in that country in medicine, as well as in other fields, is dependent upon improvement in general education, standards of living, and sanitation. The country is also handicapped by a relatively low level of political integrity.

Pathology and Mechanism of Pain of Ruptured Lumbar Intervertebral Disc: Treatment by Vertebral Body Fusion. DR. RALPH B. CLOWARD, Honolulu, T. H.

DISCUSSION

DR. PAUL BUCY: I am one of those who feel that Dr. Cloward has made a real contribution. He knows I disagree with him about some things. I think that the form of spinal fusion he describes is probably the best. It should be far superior to the usual fusion carried out by placing bone grafts on the laminae and operating on the articular facets.

I am not in a position, because of lack of experience, to comment on Dr. Cloward's statement that this is a satisfactory treatment for those patients who have only pain in the back. The principal point upon which Dr. Cloward and I disagree is when this operation, or any fusion of the spine, should be done. He feels it should be done on all patients who have a herniated intervertebral disc, and I feel it should be restricted to relatively few.

DR. RALPH B. CLOWARD, Honolulu, T. H.: I did not mean to imply that every patient has to have this operation. I do imply that, in my own experience, I would prefer to do this operation in preference to any other because it has been my experience that these patients have been cured. Of course, practicing on a small island, as I do, which is only 35 miles long, and with 2500 miles of water in all directions, I am forced to live with my patients. For 10 years I was the only surgeon in the Islands, and I did not want these fellows back on my doorstep pushing my bell. It was wartime, and these fellows were working in defense jobs and war jobs, doing heavy work. I would operate on them and they would come back and say they could not work; so I had to do something. It was because of my peculiar geographical location and because it was in wartime, I think, that this operative procedure came into being, and the volume of experience that I have had with it over the years, watching many of these patients get out and get well, and following them over a 10-year period, has led me to prefer it. The more I see of them, the more convinced I am that I am going to enjoy living with my disc cases more than a lot of other neurological surgeons.

CHICAGO SOCIETY FOR PHYSICAL MEDICINE AND REHABILITATION AND CHICAGO NEUROLOGICAL SOCIETY

Benjamin Boshes, M.D., *President, Chicago Neurological Society, in the Chair*

Oscar Sugar, M.D., *Secretary, Chicago Neurological Society*

I. F. Hummon, M.D., *President, Chicago Society for Physical Medicine and Rehabilitation*

G. Davidsohn, M.D., *Secretary, Chicago Society for Physical Medicine and Rehabilitation*

Joint Meeting, Dec. 14, 1954

Physiological Basis of Muscle Electrical Potentials. DR. GILBERT LING.

When electrodes are placed on the surface of a single muscle fiber, two types of electrical potentials are likely to be recorded. They are, respectively, the end-plate potentials and the action potentials. Both are transient variations of a steady potential difference across the cell surface, namely, the resting potential. The resting potential is therefore the physiological basis of the muscle potentials. More precise studies of such potentials have been made possible by the development of a microelectrode technique. Such studies led to possible explorations into the physical mechanism underlying the resting potential and its variations. The older "membrane theory" of Bernstein and its various other modified forms were discussed and their inadequacies mentioned. Finally, a new theory, the "fixed charge hypothesis," was presented. Electrical potentials and the unique ionic distribution inside and outside the cells, which lead to their creation, were then discussed in the light of the present theory.

General Aspects of Clinical Electromyelography. DR. Y. T. OESTER.

The techniques and instruments which are currently available for routine clinical electromyography were briefly reviewed. Methods of recording and preservation of records were indicated. A survey of the general terminology used to describe the various potentials was presented.

A description of the several types of electrical patterns which are encountered in applied electromyelography was made, with illustrative lantern slides. This included motor unit potentials of all types, fasciculation potentials, fibrillation potentials, nonspecific potentials, and so-called electrical silence.

In the concluding section, a survey was made of some of the sources of error in evaluation of electromyographic findings. These include potentials from other muscles or other tissue, air- or wire-borne electrical interference, static discharges, and many potentials which may result from faulty electronic components of the electromyograph.

The final phase of this presentation was a demonstration of typical electromyographic findings by means of oscilloscope and loud-speaker displays, from a tape recording of selected electromyograms.

Electrodiagnosis in Poliomyelitis. DR. ALEX J. ARIEFF and DR. NORMAN B. DOBIN.

Sixty-two patients with 94 paralyzed and 91 recovering muscles were examined electrically at various times, ranging from two weeks to nine years after onset of paralysis.

The examination included galvanic rheobase, polar ratio, chronaxie, repetitive stimuli (internal curves, cathodal tetanus ratio, faradic response, and electromyographic observations). The kinetics of normal denervated and regenerated muscles were reviewed.

For the most part, galvanic data were consistent with other lower motor neuron lesions, mostly root or cauda spina lesions; but the faradic response was most consistent with eventual clinical picture of recovery or paralysis.

Electromyography revealed action potentials in recovering muscles a few weeks after paralysis. None was present in the chronically paralyzed muscles in spite of severe pain. No spastic potentials were found. Fibrillary potentials were present in both groups but disappeared in most of the recovered group at the end of a year, but were present in 40% of the chronic muscles years after paralysis.

The median fibrillary denervated voltage was 100-125μv, which is greater than those usually documented. High-voltage spontaneous units were not observed in either recovering or denervated muscles.

This study should be repeated, if possible, by serial studies.

Electromyography in Primary Disorders of the Muscular System. DR. A. A. RODRIQUEZ.

All the primary disorders of muscle have in common the following electrodiagnostic characteristics: First, on testing for the response of the nerves and muscles to appropriate electrical stimuli, there is no evidence of reaction of degeneration. Second, there is no evidence of true denervation fibrillation on electromyographic sampling.

The myotonias reveal the most characteristic electromyographic findings. These include the spontaneous potentials which occur after insertion of the needle electrode and which, on the audio unit, cause a sound resembling diving airplanes. These findings readily differentiate the true myotonias from that seen in hypothyroidism.

In myasthenia gravis there is a gradual decrease in the frequency and amplitude of the motor unit potential when the subject attempts repeated or prolonged sustained contraction. Definite improvement is usually noted after administration of neostigmine.

The muscular dystrophies are characterized by persistence of the "interference pattern," an increased proportion of polyphasic units, a reduction in amplitude, and a shortened duration of the individual unit.

Benign myokymia may be differentiated from diseases affecting the anterior horn cells by the absence of denervation fibrillation voltages. The fasciculation potentials of myokymia are discrete diphasic or triphasic in form and differ somewhat from those seen in anterior horn cell disease.

Electromyography is a useful aid in the diagnosis of primary muscular disorders. It is not a substitute for a good history and examination.

DISCUSSION

DR. NORMAN DOBIN: Since most of the program tonight was listed under electromyography, Dr. Arieff and I thought we should look over our own material and compare the information elicited by electromyography with that by electrodiagnosis in the same patient. I might add that, like Dr. Pollock, we consider the two diagnostic aids complementary to, rather than in competition with, each other. We also usually do more than one sampling of a given muscle during the electromyographic examination.

We reviewed the records of 591 patients examined by us at the Veterans Administration Hospital, Hines, Ill., for electrical signs of lower motor neuron disease. Such signs were detected with the aid of electrodiagnosis in 57% of the patients and by electromyography in 33%. In a group of 260 patients with peripheral nerve lesions, including neuritides of varied etiologies, electrical signs of lower motor neuron disease were elicited in 76% by electrodiagnosis and in 42% by electromyography.

In another group, of 42 patients, consisting of 27 patients with amyotrophic lateral sclerosis, 11 patients with progressive muscular atrophy, and 4 patients with Charcot-Marie-Tooth disease, electrical signs of a lower motor neuron lesion were detected in 52% of the patients by electrodiagnosis and in 33% of the patients by electromyography.

In a group of 16 patients with the diagnosis of myotonic dystrophy, 10 patients, or 66%, showed myotonic buzzing induced spontaneously by needle insertion or tapping the muscle. In a previous study of ours, 80% of the muscles examined showed this reaction. The potentials are narrow, not over 1 msec. in duration. In the same group of patients galvanic studies showed the following abnormalities: In 80% of the cases the chronaxie was elevated; the tetanus ratio was less than 2, and there was a decreased speed in contraction. The strength-duration curve was abnormal in most, and the strength interval in 65%, of the patients.

In a group of seven patients with muscular dystrophy the chronaxie was elevated in 35% and a diminished response to faradism was present in 50%. Electromyography showed narrow low-voltage units.

Thus, it is obvious that in evaluating the electrical signs of neuromuscular disorders, a complete electrical examination should include galvanic and faradic stimulation, as well as electromyography.

I should like to comment on Dr. Oester's paper. Dr. Oester states that interference patterns are normally seen but are too complex to analyze. The picture is really not a complex one, if it is only remembered that voltages seen are summations of individual muscle voltages produced as the muscle contracts at different times about the electrode area.

Dr. Oester also showed a photograph of what he calls a fasciculation voltage. This picture does not at all resemble the fasciculation voltages ordinarily observed by us. Fasciculation

voltages are not complex units, as shown, but, rather, simple ones, resembling a single motor action potential, such as may be obtained by a minimal voluntary effort contraction, and are not as long in duration as the unit shown by Dr. Oester.

Among the EMG artifacts mentioned in Dr. Oester's presentation are potentials which he states may be produced by other tissues in the body. I know of no tissue, other than muscle, which will present the potentials seen in electromyography. That is, it must be a contractile type of tissue and produce an electrical type of reaction. Pulsations of a small blood vessel in the vicinity of the electrode may be recorded. The rubbing of the needle electrode against bone or fibrous tissue will also give an artifact.

DR. Y. T. OESTER: I feel that I should answer a few of Dr. Dobin's comments. I agree quite completely that the term "interference" is a poor one, but the literature contains it and it occurs in the field. I concur in the statement that we should define our terms.

In regard to the form of the electromyograph when the potential is a fasciculatory type, the forms we have frequently seen are complex potentials. On the other hand, I do not believe that the complex potential is an average response, or a normal response. But, occasionally, we will see a complex potential. Finally, concerning the comment by Dr. Dobin about other tissues, it is difficult to spell out whether or not the potentials are from the blood vessels and nerve fibers (noncontractile tissue) in the neighborhood of the muscle.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

E. Jefferson Browder, M.D., President, New York Neurological Society, Presiding

Joint Meeting, Oct. 11, 1954

Presidential Address: Parkinson's Disease: The Tremor-Mediating Mechanism. DR. E. JEFFERSON BROWDER and DR. HARRY A. KAPLAN.

Observations during and following operations on the central nervous system in humans for relief of the tremor and rigidity of Parkinsonism have disclosed functional changes which seemingly have advanced our knowledge concerning the abnormal neural mechanism of this disease.

The operative procedures performed in our clinic which have altered tremor and rigidity are undercutting and/or excision of Brodmann's Area 6 (4 cases); section of the anterior limb of the internal capsule (32 cases); section of the pallidofugal fibers (2 cases); partial section of a cerebral peduncle (2 cases); section of a lateral pyramidal tract of the spinal cord (3 cases), and occlusion by electrocoagulation of an anterior choroidal artery (5 cases).

Surgical ablation of the motor cortex, section of a pyramidal pathway in the cerebral peduncle, and division of a pyramidal pathway in the upper cervical spinal cord, all result in loss of tremor and rigidity, but with severe paresis to paralysis of the extremities affected by the procedures. Return of motor function is accompanied by return of tremor, rigidity being largely replaced by spasticity. Section of the fibers of the anterior limb of an internal capsule, as well as section of pallidofugal fibers unilaterally, results in loss of tremor and rigidity without enduring paresis. Electrocoagulation of an anterior choroidal artery may reduce tremor and rigidity without enduring paresis. In some patients a unique and important feature following this surgical procedure is a reduction in the rate of tremor (in the extremities contralateral to the artery occluded) to exactly one-half its preoperative rate and one-half the rate of the opposite side.

From these data one may postulate a controlling mechanism for the tremor of Parkinsonism within the subthalamic area. Furthermore, two arms of a tremor-mediating mechanism have been demonstrated, one by way of the pallidofugal fibers and the anterior limb of the internal capsule, and the other through the corticospinal pathway.

The paper will be published in full elsewhere.

Medical Treatment of Parkinsonism. DR. H. HOUSTON MERRITT.

Parkinsonism may follow injury to the nervous system by a variety of disease processes and noxious agents, or it may develop without any known disease or injury to the nervous system. Symptoms may follow injury to the nervous system by trauma, carbon monoxide intoxication, or manganese and other metallic poisonings, or they may develop in elderly persons who have cerebral arteriosclerosis. All of these conditions are responsible for only a small percentage of the cases. Parkinsonism was a common sequel of damage to the nervous system by the epidemic

of encephalitis lethargica in the years 1918 to 1923. Although Parkinsonism may develop many years after the acute attack of encephalitis lethargica, few new cases are seen at the present. At the present time the cause of the symptoms in the majority of patients is unknown. The cause of this so-called idiopathic Parkinsonism can only be conjectured. It is possibly the result of a metabolic defect or injury to the nervous system by endogenous or exogenous toxins.

In the absence of any known etiology, no rational therapy of the disease can be advanced. We can therefore only attempt to alleviate the symptoms.

The symptoms of Parkinsonism are quite varied, but the two most disabling features of the disease are rigidity and tremor. It is probable that rigidity is the cause of greater incapacitation than tremor.

Attempts to alleviate tremor or rigidity by pharmacologic agents which are known to modify transmission at the myoneural junction or influence conduction at synapses within the nervous system have not been attended by any significant results. Curare, quartenary ammonium salts, or such compounds as Myanesin do not alleviate the symptoms of Parkinsonism in doses which do not produce paralysis. The present-day treatment is therefore entirely empirical.

At present the various alkaloids of the belladonna root are the mainstay in therapy. Synthetic compounds with physiologic actions similar to those of atropine have recently been introduced into therapy. Among the latter are Artane, Panparnit, and Pagitane. Favorable results have also been obtained with various combinations of these drugs with the belladonna alkaloids and with the antihistamines. Alleviation of the symptoms due to rigidity is more apt to occur than a decrease in the tremor.

DISCUSSION

DR. MURRAY E. MARGULIES: I would like to ask whether Dr. Merritt has had any experience with Pagitane, and, if so, what results he had.

DR. H. HOUSTON MERRITT: I have had only a limited experience with Pagitane, but Dr. Doshay has made an extensive study of this compound.

DR. LEWIS J. DOSHAY: We commenced studying Pagitane two years ago, and we have over 200 cases using the drug at the Vanderbilt Clinic and among private patients. Dr. Zier and I reported (Zier, A., and Doshay, L. J.: *Neurology* **4**:682, 1954) a month ago a series of 142 cases showing good results with Pagitane. Its chemical structure is almost identical with that of Artane, and it is an excellent preparation. In some patients it causes less dryness reaction than Artane and is slightly more potent. It has a cerebral-stimulating action, and it seems to cause less mental confusion. Some of the older patients develop hallucinations with other drugs, but we have not seen such reactions with Pagitane, even in large doses. It is a good drug to turn to when patients tire of Artane or fail to respond to it for one reason or another. It controls tremor, oculogyria, and rigidity, and we think it is a good addition to the armamentarium for Parkinsonism.

DR. ABRAHAM M. RABINER: Conclusions arrived at from observation and follow-up of patients with Parkinsonism in an outpatient department as to the value of medicinal therapy are not as reliable as studies on patients confined in a hospital for chronic disease. Patients' statements as to how they were during the preceding week should not be used in a statistical study unless accompanied by more accurate objective studies.

I again stress the fact that rigidity of Parkinsonism becomes severer if the patients are inactive, whereas activity lessens rigidity already present and retards the tendency to increasing rigidity. And so, consistent with the cardiovascular status, patients with Parkinsonism must not remain seated or lie in bed for long periods, but should be as active as possible. They are like water which freezes when still, whereas moving water has a less marked tendency to freeze.

Psychiatric Experiences with Painful Phantom Limb. DR. LAWRENCE C. KOLB (by invitation).

The study dealt with an attempt to identify the psychological processes and emotional states contributing to the painful phantom phenomenon. Twenty-seven amputees with this condition were studied through psychiatric interviews. Of this group, 22 complained of pain, presented evidence of emotional disturbance, but had no evidence of physical disease, while 5 showed indication of physical disease of a neurologic, vascular, or arthritic variety.

A comparison of the life adaptation of these persons, their pain syndrome, and their responses to emotionally disturbing events allowed the clinical differentiation of the two groups. A number with emotional disturbances were found to have the painful complaint evoked by

references to persons and events disturbing to the particular patient. A high percentage were found to have had a close association with another amputee in the past (interpreted as a hostile identification), as compared with similar associations in healthy, psychoneurotic, and neurotic groups. Anxiety in such amputees was found to modify their perception of their environment, as shown by their responses in psychologic tests and also by their subjective reports of perception of other persons as amputated. They tend to project their own defect externally. Certain ones tended to deny their defect. The dream life of the patients was either wish fulfilling or repetitive of the traumatic event. The relationship of mourning over the amputated part to the problem of psychogenic pain was discussed. The value of properly preparing amputees for operation was indicated.

A brief psychotherapeutic technique was used successfully in the treatment of patients with the acute painful phantom syndrome. The following significant topics were penetrated in successive order from the initial interview in this therapy: (1) the patient's concept of the phantom limb phenomenon and any attendant rationalization that he may have in regard to the occurrence of this phenomenon: (2) his wishes and fears in regard to the care and disposal of the amputated part, and (3) the significance of his present and past attitudes toward his body in relation to his real and fantasied experiences with persons (parents, family, and associates) significant to him.

DISCUSSION

DR. CARLOS G. DE GUTIERREZ-MAHONEY: I am very happy to take this opportunity to extend a public professional welcome to Larry Kolb. We are extremely fortunate that he is now with us in this city, and I am sure we will all gain benefit in more fields than the field of the phantom through his counsel and help.

I am happy to confess that one of my failures led to this monograph with which Professor Kolb presented us, and which I have read with a great deal of interest. The problem of the phantom, I presume, will continue to be a phantom problem in spite of the erudition of workers of Professor Kolb's capacity. I think it important that he again calls attention to the psychological aspect of the phantom, since we who work in more tangible fields tend to neglect the importance of these things.

DR. MORRIS B. BENDER: I would like to ask Dr. Kolb whether he had any similar psychiatric experiences in patients with causalgia. I am sure you know that many patients with causalgia show reactions similar to those with phantom limb; yet these patients are often relieved by cervical sympathectomy, and rarely do they show a recurrence following this procedure.

DR. LAWRENCE C. KOLB: I decided not to discuss the neurophysiology or the surgical substrate of these particular problems, and I trust from my remarks that all of you are aware that I recognize that certain patients do have neurologic as well as medical problems underlying the painful conditions—certainly patients do, but a rather small proportion.

In regard to the problem of causalgia, it seems to me the patients who have come to us fall into two groups: There are those who fit the description of this condition as given by Weir Mitchell, and all those others who fail to do so. In the first group I have seen none who have been benefited by psychiatric treatment.

A New Method in Electrocerebral Therapy and Research: Monopolar (Unipolar) Electrocerebral Stimulation—Subconvulsive and Convulsive. DR. JOSEPH EPSTEIN.

On the basis of experimentation and research for the past year, it was determined that therapeutic electric stimulation can be effected through the intact skull by unipolar or monopolar introduction of current. We believe that in this manner selected areas of the brain can be treated. It is also felt that the current thus introduced reaches the reticular activating substance and the brain stem. We think that the conventional bipolar placement of electrodes, particularly over the frontal and temporal regions, requires very much more current to produce a convulsion and causes excessive stimulation of the frontal lobes. This latter situation is probably responsible for the memory changes, amnesia, confusion, and anxiety states shown by many patients who receive electroshock treatments with bipolar placement of electrodes. The method which we have described utilizes an indifferent bracelet or cuff type of electrode applied to the right forearm. The active electrode is applied manually to selected areas of the skull. The unidirectional, spike wave, pulsating type of current is used in this work (Reiter apparatus CW 47C). In the subconvulsive treatment three frontal zones are stimulated bilaterally, the treatment cur-

rent remaining under constant control of the operator. The average treatment for subconvulsive stimulation is 5 ma. for 7 to 10 seconds. When grand mal convulsions are administered, the active monopolar electrode is applied near the vertex of the skull. Convulsions are produced within a few seconds, and with current values and duration periods a fraction of those heretofore necessary. The average treatment current for convulsions is 10 to 12 ma. for two to five seconds. Patients show no memory changes as a result of this treatment. Up to the present time, no complications of physical or mechanical nature have been encountered. We also have reason to believe that the danger of organic injury to the brain is eliminated because of the minimal current values utilized. On the basis of preliminary studies, we believe that the clinical results of this treatment will equal those now obtained by conventional methods and the complications and disadvantages of the latter will be largely eliminated.

DISCUSSION

DR. GEORGE H. HYSLOP: I think that before Dr. Epstein completes his work in this field it would be a good idea for him to go into the literature and read on the experimental work on the threshold of tissues for irreversible changes due to current transmitted, as well as the pathways in which current is conducted. There is practically no diffusion between the point of entrance and the point of exit; and the course is as direct as can be. When it comes to a current of 30 ma. in nerve tissue, it takes about five seconds to produce temporary damage, and 40 ma. causes irreversible damage.

DR. LOTHAR B. KALINOWSKY: This type of work represents interesting and necessary research, and it should remain research until final judgment can be passed on it. In his first publication, Dr. Epstein recommended it as a treatment which seemed to replace the standard Bini-Cerletti therapy, but now convulsive treatment with monopolar stimulation is added. I personally cannot see why low current intensity should change the type of convulsion, because convulsions are a one-or-none response and once the convulsion has started, it runs its course. We can only modify the onset, and we can suppress the clonic phase by means of continued stimulation, as has been done also with the so-called electronarcosis. But this can be done with any type of current; and as long as we use convulsive intensities, we are apt to have fractures which occur with the unidirectional current, as well as with the so-called electronarcosis, which is only a modified convulsion. The nonconvulsive current did not prove its value, and I cannot see why unipolar application should make it more effective.

The question of hypothalamic stimulation is a very interesting one. But we still have no proof that it works.

DR. DAVID J. IMPASTATO: I had the pleasure of discussing Dr. Epstein's paper earlier this year in St. Louis, when he described his monopolar nonconvulsive technique; and I think he should be congratulated on having had the courage to initiate this fine piece of research. It certainly took a lot of courage to treat a patient with an electrode on his head and one on his right forearm. Most of us would not have dared to do this, although we knew that in his early studies on epilepsy in dogs Cerletti had placed one electrode in the mouth and the other in the anus.

We are mainly interested in the monopolar method not from the point of view of fractures, but, rather, from the possibility of better clinical results, either quantitatively or qualitatively. At present we feel that this method of electroshock therapy is merely exploratory.

DR. MORRIS B. BENDER: What are the results with this method of treatment? Are they superior, equal, or inferior to the conventional, or unidirection method?

DR. JOSEPH EPSTEIN: First, as to the results of treatment: We have been using this method for a little less than a year. Our figures are not complete. We feel that with the convulsive method the results are about the same as with the other convulsive methods.

Dr. Hyslop's comments and figures are based on currents applied directly to nerve tissue. My work is based entirely on currents applied through the intact skull. The two are not comparable in any way.

I would like to take issue with Dr. Kalinowsky in this way: I think Dr. Kalinowsky is a die-hard. He was one of the early users of the Bini-Cerletti method, and he is sticking to it, refusing to recognize the benefits of its modifications. He is very much like Dr. Sakel, who introduced the method of insulin shock, and he is going to stick to it without modification.

It is not scientifically valid to state that once a convulsion ensues, the same complications are bound to occur. All evidence is to the contrary.

Dr. Kalinowsky asked about Sodium Amytal. We use it only in the nonconvulsive treatments; we do not use it in the other, and I think perhaps he is right—perhaps the sedative has an effect in causing some improvement.

Morris B. Bender, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*
Joint Meeting, Nov. 9, 1954

Vasodilatation, Lowered Pain Threshold, and Increased Tissue Vulnerability Due to Peripheral Nervous System Effects. Dr. Frank N. Bilisoly Jr. (by invitation), Miss Helen Goodell (by invitation), and Dr. Harold G. Wolff.

The area of vasodilatation in the skin (flare zone) of the axone reflex was utilized to study the thesis that as a result of peripheral nerve action alterations occur in the tissue supplied that either damage it or make it more susceptible to injury.

It was demonstrated that the pain threshold in the flare zone of the axone reflex is lowered during the process of spread of the flare.

It was also shown that this lowered pain threshold is a manifestation of increased tissue vulnerability, so that not only do previously non-noxious stimuli become noxious but mildly damaging stimuli become more damaging.

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DISCUSSION

Dr. Harold G. Wolff: I would like to speak of the method. Obviously, we would like to draw implications from these experiments; we would like to be able to say that the nervous system, perhaps in a variety of ways, participates in tissue damage. Unfortunately, the only model we could think of to test this thesis was that described, the situations presented by the axone reflex. I want to be sure that all share an understanding of what has been done. One injured the skin in several ways—by electric current, by acid, and mechanically. Then one disregarded the area injured and studied the area of "flare," which surrounds and spreads anywhere from 2 to 3 to 10 cm. from the site of injury. It is the occurrence of this flare area that is dependent on dorsal root fibers. In the absence of dorsal root fibers one gets a circumscribed local tissue change at the site of injury, but not the large area of vasodilatation. It is this latter area which we have been measuring and analyzing, and which demonstrates the lowered pain threshold. To what extent autonomic fibers participate in such areas, to what extent other fibers do, we do not know. We do not know whether the axone reflex participates in any physiologic way other than that associated with the vasodilatation. Suffice it to say, the argument now stands that the nervous system has been shown by the evidence presented to possess an equipment which can modify the integument of tissue.

Dr. M. Bornstein: I would like to ask if you had occasion to study a patient who by chance or by operation had had dorsal root fibers cut, in whom an injection could be made into the skin, and the area around that injury studied by pinprick. If you injected histamine, did you fail to get the flare?

Dr. Harold Wolff: There was no flare. We have done this repeatedly in patients who have had a peripheral neurectomy. If we were studying the leg, or the foot, or the arm, we found we could estimate the degree of return of function of a regenerating nerve by the size of the flare around an intradermal injection of histamine. As recovery proceeded, in the more distal portion there was no flare; in the more proximal portion there was a large flare, and as the patient recovered the flare occurred more and more distally. Observations made on the scleral portion of the eye in rabbits following dorsal root section have demonstrated relatively minor response to inflammatory agents. I do not think there is any doubt at all but that the integrity of the dorsal root fibers is necessary for the flare effects with local injury. The dorsal root fibers must be intact. Immediately following section the flare reaction is observed, but if you wait a few days so that the dorsal root fibers degenerate, then the flare, or axone reflex, is absent.

Dr. M. Bornstein: What I meant was this. In those cases where there was no flare, which you know is due to the integrity of the dorsal root, if you inject histamine to get the local reaction, what is the effect 10 cm. away?

DR. FRANK N. BILISOLY: Outside the flare one gets results which are comparable to the control state; here you are dealing with undisturbed tissue, and you find higher pain thresholds than when you move a few centimeters toward the injury, and into the flare zone.

DR. HAROLD WOLFF: Has anyone in the audience any suggestions as to another way by which to approach this problem?

DR. FRANCIS ASBURY ECHLIN: I wonder if any of the neurosurgeons have repeated the observations of Foerster (*Festschrift für Rossolimo,* 1925) on stimulation of the distal end of a cut dorsal root, in which he produced burning pain and hyperalgesia in the distribution of that root. He found that when he cut the roots on either side of the one he stimulated the pain disappeared. In other words, the stimulation of the root did what Dr. Wolff and his colleagues have shown: It sent impulses apparently out through the afferent fibers and did something to the sensory receptors which made them more susceptible to stimulation of the skin, and this effect was abolished when he cut the neighboring posterior roots.

DR. HAROLD WOLFF: The burning pain disappeared, but the vasodilatation was there, even if the posterior root fibers were cut, as long as the afferent fibers of the part stimulated were intact. Dr. Pool has made observations some years ago which were similar.

DR. J. LAWRENCE POOL: The observation to which Dr. Wolff referred has since been corroborated by others: When the ulnar nerve was cut, for example, by bullet or shell wound during World War II, a chronic separation of the ulnar nerve in the forearm might occur, leaving a gap of 4 or 5 cm. in nerve continuity. After the distal stump of the nerve was dissected and isolated (for repair), under local anesthesia, and stimulated mechanically or electrically, the patient would complain of pain in the adjacent, or median, nerve. The same phenomenon occurred if the chronically separated distal stump of the median nerve was stimulated: The patient would then complain of pain in the adjacent intact ulnar nerve. In these isolated distal nerve stumps running down to the hand, nothing should be viable according to expectations; yet when we stimulated or gently pinched it, the patient experienced pain in the adjacent intact nerve. We have blocked the median nerve and again stimulated the adjacent distal ulnar nerve stump, and then found pain referred to the radial nerve distribution. Sections from these distal stumps showed, we thought, a few myelinated and nonmyelinated nerve fibers. Whether these fibers represented retrograde regeneration of autonomic fibers we could not, of course, tell. This was a real phenomenon that we cannot explain and, unfortunately, could not pursue further (Pool, J. L.: Nerve Stimulation in Paraplegic Patients by Means of Buried Induction Coil: Preliminary Report, *J. Neurosurg.* **3**:264-267, 1946). Perhaps it may tie in with some of your work, Dr. Wolff.

DR. FRANCIS ASBURY ECHLIN: May I ask whether in your experiments you have any evidence to substantiate or refute Sir Thomas Lewis' idea of a pain substance being liberated after tissue injury (Lewis, T.: Pain, New York, The Macmillan Company, 1942), and whether it is this substance which renders the sensory receptors in that neighborhood supersensitive?

DR. HAROLD WOLFF: We do infer that there is a liberation of substances in this damaged tissue which lowers the pain threshold. According to the work of Armstrong on blister fluid, it is not histamine; it is not acetylcholine, and it is not a change in the electrolyte concentration, but it seems to resemble serotonin.

Deep Frontal Stimulation with Implanted Electrodes. DR. J. LAWRENCE POOL and (by invitation) DR. WILLIAM K. CLARK.

Pain was effectively relieved for periods of two to four weeks in two patients in whom small electrodes were placed at or close to the midline just anterior to the rostral extent of the third ventricle. Pain was not relieved in two other patients in whom the electrodes were placed in the frontal lobe white matter at a more rostral or lateral position.

In the fifth patient (schizophrenia plus carcinomatosis) the psychotic state seemed definitely improved after stimulation. This patient did not show evidence of pain before or after electrode implantation.

Pain relief was judged subjectively by the patient's statements and attitude, and objectively by a considerable, lasting reduction in 24-hour narcotic requirements.

Pain relief was spoken of by the first two patients as soon as the small current (3 to 4 ma.) was turned on. Control stimulations did not have such an effect. Since certain physiologic effects and pain relief could be obtained on repeating stimulation weeks later, it is felt that the stimu-

lation, rather than any tissue damage, was responsible for the effects. No ill-effects or distress attended these stimuli, and no infections occurred in the five patients in whom electrodes remained in place for four or more months.

DISCUSSION

DR. JOSÉ M. R. DELGADO: I would like first to congratulate Dr. Pool and Dr. Clark on this most exciting presentation and then to make some comments. We have been working with depth electrodes in monkeys and cats since 1948, and in human patients since 1951.

We have had an opportunity to study 22 patients in collaboration with Dr. Hannibal Hamlin and Dr. Yale David Koskoff. Of these, four had intractable pain, in two of whom it was thalamic and in the other two tabes dorsalis. In two of the four patients we were successful in relieving the pain by destruction of small areas within the frontal lobes. We have had no pathologic examinations of any of these patients.

During the past year, in collaboration with Dr. H. Enger Rosvold, we have studied some of the functions of the frontal lobes in the monkey. It was known that delayed-response-test performance, but not discrimination-test performance, was severely and invariably impaired after frontal lobotomy. Other symptoms, such as hyperactivity, circling, and changes in docility and in eating behavior, may also appear after lobotomy. In our studies we have shown that these same effects can be produced by electrical stimulation or destruction of a very restricted area of about 2 mm. in diameter, at the level of the most anterior portion of the head of the caudate nucleus. Stimulation or destruction of other areas of the frontal pole did not produce such effects.

DR. ALEXANDRA ADLER: When comparing the method of deep frontal stimulation with that of intracerebral procaine injection for the treatment of intractable pain, will Dr. Pool please comment on the main differences as to the effect and state which method would be preferable from the practical point of view?

DR. HAROLD G. WOLFF: Will Dr. Pool tell us the duration of stimulation and the effects observed when testing patients after deep frontal stimulation with pins or on squeezing a muscle?

DR. J. LAWRENCE POOL: In reply to the first question: I have not done any of the procaine injections, but I have talked to Dr. Frank Nulsen, of Cleveland, who has done considerable work of this kind. He tells me that the effects he gets from procaine injections into frontal white matter are about the same as the effects we have reported tonight.

In reply to Dr. Wolff's question concerning the time relation of stimulation: We have shown a long chart indicating the different types of stimulation that we tested. The effective period of stimulation was about 60 seconds and the usual effective current 3 to 4 ma.

DR. HAROLD WOLFF: What about testing a patient for reaction with a pin?

DR. J. LAWRENCE POOL: We did not do that. We were simply observing different physiologic effects and nothing else to interfere with the picture during the period of stimulation.

DR. HAROLD WOLFF: Did the reaction to other kinds of noxious stimuli change?

DR. J. LAWRENCE POOL: As far as I know, it did not. At the time of stimulation we did not test for pain perception.

DR. HAROLD WOLFF: When asked about their original pain, did they think it was just as bad?

DR. WILLIAM K. CLARK: Two patients had complete relief of pain for three to four weeks each. They said they felt "wonderful" during that time. They had no difficulties, and the limitation of motion which had been present before our treatment disappeared. Later, when pain recurred, these patients reported they were just as uncomfortable as before. In one case we had good results during the first stimulation, while later stimulations did not do anything. This patient complained of the same pain and did not show objectively any apparent difference in complaints.

Psychodynamics of Depression. DR. MORTIMER OSTOW.

Depression is an affect which appears either in response to the loss of a love object or in anticipation of some act which would result in the loss of a love object. The characteristic psychic and physical components of the depression syndrome can be understood as a device to compel protective acts on the part of those who love the patient. When depression follows an externally imposed significant loss, it may be considered normal. When it follows no loss or a trival loss, it is pathologic. In such a case the depression is provoked by the unconscious fantasy that a wish to destroy or injure the love object has been realized. However, the ensuing depression is usually

not successful in terminating the hostile tendency, which continues to express itself against love objects in passive and indirect ways and, because of the guilt which the aggression evokes, reflexively in self-destruction.

DISCUSSION

DR. PAUL FRIEDMAN: I feel flattered to have been chosen by Dr. Ostow to discuss his paper. You all share my opinion, I am sure, that he has given us a lucid, concise survey of this very difficult and complex subject. I was more privileged than you, since I was able to read the full text of the paper, which he could present here only in part. He succeeded in reviewing all the important psychological mechanisms that are involved in the dynamic process of depression: identification, introjection, guilt, and, above all, the vicissitudes of aggression. However, I cannot resist referring to one of the earliest illustrations of the most pathognomonic mechanism of depression, namely, introjection.

In recent times it has been speculated, in some analytic quarters, that electric shock might produce a violent motor discharge of aggressive tension. I wonder if sufficient data have been collected to substantiate this speculation—in other words, if the suicidal tendencies really have been found to subside after the administration of electroshock? I wonder if Dr. Ostow would care to comment on this question.

DR. MORTIMER OSTOW: Dr. Friedman asked whether one can make a statement that electric shock discharges aggressive tensions. I doubt that electric shock therapy has any specific effect in dissipating aggressive tendencies. It is my impression that whole psychic constellation, which includes depression as its affect, is dissipated by the electric shock.

Transference Problems in Connection with Shock Treatments and Psychosurgery. DR. LOTHAR B. KALINOWSKY.

Psychiatrists applying somatic treatments and psychoanalysts are so far apart in their concepts that studies to evaluate phenomena like transference and countertransference during somatic treatments have never been undertaken. Insulin coma treatment, electric convulsive treatment, and psychosurgery offer interesting, but quite different, problems in this respect. Insulin coma treatment is that type of somatic therapy during which a rapport between physician and patient can be best established. Many clinicians feel that the patient's attachment to the physician is an important factor for the results obtained, but this has never been proved. In electric shock therapy the psychopathologic manifestations differ from the hypoglycemic state because the patient immediately falls into a deep unconsciousness, has an amnesia for the whole procedure, and the psychotherapeutic situation is further complicated by the ensuing confusion. Electric shock therapy has been considered as a mere adjunct to psychotherapy. Although it is possible to make patients more accessible to psychotherapy by means of two or three electric shock treatments, attempts to improve transference by this method are unsatisfactory. Psychosurgery changes the psychotherapeutic rapport with the patient by the modification of his emotional state and by the personality changes in the sense of a frontal lobe syndrome.

DISCUSSION

DR. PAUL H. HOCH: I think Dr. Kalinowsky gave a very good and very complete review of the rapport situation in patients who receive shock treatment or who undergo psychosurgical procedures. I cannot add very much to his discussion. I would like to remark that, unfortunately, our psychotherapeutic attempts are not very fruitful in those patients who receive all kinds of psychiatric treatment with failure and are operated on and the operation fails, and then, after an operative failure, undergo psychotherapy. Here usually psychotherapy does not produce more than it produced before the operation.

E. Jefferson Browder, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, Dec. 14, 1954

Distant Ischemic Lesions with Cerebral Aneurysm. DR. IRWIN FEIGIN.

Congenital cerebral aneurysms commonly cause lesions by rupture into the subarachnoid or subdural spaces or into the substance of the adjacent brain, or by compression of adjacent tissues when the aneurysm becomes large. More rarely, distant ischemic lesions may occur. These may be found in the distribution of the artery on which the aneurysm is located. In such case, it may be postulated that the aneurysm itself, or the surrounding hemorrhage following rupture, may partially compress the vessel, so that blood flow becomes inadequate and encephalomalacic

changes may occur in critically deficient tissues. It is also possible that small emboli may pass into the vessel from a thrombus within the aneurysm and block a distal branch, causing encephalomalacia. In other cases, in which the aneurysm has caused increased supratentorial pressure, a herniation of one or both unci through the tentorial notch may cause lateral compression of the midbrain and narrow or block some of the vessels to the brain stem, causing hemorrhages and softening in the midbrain or pons. Similarly, one or both posterior cerebral arteries may be narrowed, causing encephalomalacic changes in the occipital lobes. Uncal herniation with these sequelae is more commonly described with neoplasms. Two illustrative cases were presented.

DISCUSSION

DR. SIDNEY W. GROSS: Dr. Feigin's presentation calls attention to another important lesion which may be associated with a cerebral aneurysm. It is commonly thought that rupture of a cerebral aneurysm means blood pouring out into the subarachnoid space. Actually in most patients, in addition to the rupture of the aneurysm, there is nearly always an associated intracerebral lesion at the site of rupture. In aneurysms of the anterior communicating artery it is common for the aneurysm to rupture into both frontal lobes and to produce bilateral abnormal signs. Dr. Feigin calls attention to compression of the posterior cerebral arteries due to aneurysm where there is increased intracranial pressure and uncal herniations. He does not imply that this effect is unique to intracranial aneurysms. He showed a tumor in which this occurred also. Uncal herniations occur in traumatic situations as well. Emboli breaking off at the site of the aneurysm and producing lesions at a distance have been alluded to. Whether or not this occurs remains to be proved, but it is a possibility. Blood in the subdural space with intracranial aneurysms has been encountered on several occasions. Whether or not spasm occurs along the course of a cerebral vessel which harbors an aneurysm is still unproved, although there is some evidence that it does. An aneurysm which arises near the take-off of the middle cerebral artery may produce spasm along the entire course of the middle cerebral artery and thus produce symptoms at a distance.

Pneumoencephalographic and Neurologic Study Following Psychosurgery. DR. MARCUS P. ROSENBLUM, DR. LEROY BARNES (by invitation), and DR. WILLIAM EHRLICH (by invitation).

A study was made of 100 chronic psychotic veteran patients, mostly suffering from schizophrenia, who underwent the routine type of prefrontal lobotomy (Lyerly-Poppen modification). Seizures developed in 30% of this series, and, of this number, 25 were selected for pneumoencephalographic and other studies; these formed the basis for this study. Sixteen patients (64%) suffered a maximum of one to four seizures. However, four other patients developed status epilepticus. Seventy-two per cent of the entire series developed seizures within nine months following prefrontal lobotomy. EEG studies disclosed 8 patients with focal EEG abnormalities, predominantly in the frontal lobes; 13 with nonfocal EEG abnormalities, and 4 with a normal EEG. Three patients had persistent neurologic disability of a nonincapacitating type. Pneumoencephalographic studies disclosed characteristic and predominant dilatation of the anterior horns in all the patients. In addition, 6 of the 25 patients suffered from porencephaly at the site of lobotomy. Comparison of postlobotomy air studies and nonlobotomy air studies for a variety of neurologic disorders emphasizes preponderant dilatation of the anterior horns of the lateral ventricles.

DISCUSSION

DR. JACK LONDON: Would you have any statistics which would show whether the anterior horn was cut at the time of operation? If so, did those patients develop porencephalic cysts or show any other abnormalities?

DR. ALEXANDRA ADLER: Since this investigation concerns patients who had epileptic seizures, I wonder whether the dilatation of the anterior horns might be related to that specific group; in other words, whether you should assume, or whether you have any indication, that this dilatation of the anterior horns would be present in patients without seizures.

DR. JOSEPH RANSOHOFF: I think this series has a rather high percentage of seizures following lobotomy procedures. Dr. Hoch, I believe, will correct me if I am wrong, but I think that our incidence at the Psychiatric Institute is somewhere around 10%, and we have had 300 cases. I wonder whether the use of the sucker to do the lobotomy might not be incriminated both in the production of the porencephalic defect, which was so beautifully demonstrated, and in the high seizure incidence.

DR. STANLEY LESSE: I would like to suggest the possibility that the large percentage of seizures presented here might in part, be due to the fact that the lateral cuts were not done under direct observation. I wonder if you are not actually cutting into the gray matter when you do these lateral cuts. In reality, there is very little left of the frontothalamic fibers lateral to the medial cut, and any blind lateral sweep has great likelihood of cutting into the gray matter of the convexity.

DR. PAUL H. HOCH: I also found the percentage of seizures in Dr. Barnes's cases relatively high. As Dr. Ransohoff has mentioned, in our material at the Psychiatric Institute the seizure incidence in the lobotomies is about 10%. I would like to ask Dr. Barnes if all the lobotomies performed in his cases were made at the coronal plane or anterior to it, and how the seizure incidence in his material relates to the place of a cut coronal or precoronal in localization.

DR. MARCUS P. ROSENBLUM: With reference to the higher incidence of seizures, one is able to detect convulsions more readily in patients under careful hospital surveillance. Seizures frequently occur at night, and unless these are observed they may be omitted in the report of patients at home. Thus, the hospital setting provides greater opportunity for accurate survey of postlobotomy seizures.

DR. WILLIAM EHRLICH: We do not have any definite statistics on the number of times the anterior tip of the ventricle was entered. When this occurred, it was noted on the operative records; I am sorry to say, this point is not investigated for this work. As well as I can recollect, one ventricle was entered in about one-tenth of the cases. I might say that the postoperative course, when this occurs, is about the same as in those cases in which it does not occur.

In reply to the question as to where the leucotomy incision is made: We try to make it just anterior to the coronal suture. The 1-inch trephine opening is made directly over the suture line, and the incision in the cortex is made in the center of the gyrus directly anterior to it. However, sometimes the direction of the gyri and the location of large blood vessels make it necessary to make the incision farther forward or backward. The lateral recess has not been cut since May, 1953, since which time the leucotomy incision has been limited to the mesial two quadrants.

DR. LEROY BARNES: There were two questions I should like to comment on: As concerns the findings in air studies on postlobotomy patients who did not have convulsions, we had pneumoencephalograms on only a few such patients. They showed changes similar to those in the patients with convulsions. Unfortunately, as we began our studies on the patients with convulsions, we have not had air studies on enough of the nonconvulsive patients to get definite information. So far it would appear to me that they show the same changes.

As concerns the operations entering the anterior horn, I checked the operative notes on the cases of porencephaly, and in none of them did I find a statement that the anterior horn had been entered.

Investigations on Chlorpromazine in Psychiatric Practice. DR. PAUL H. HOCH, DR. JAMES P. CATTELL (by invitation), DR. SIDNEY MALITZ (by invitation), and DR. STANLEY LESSE (by invitation).

The paper discussed the clinical use of Thorazine on inpatients and ambulatory patients. Statistics were presented indicating that of 42 outpatients who were very carefully studied and observed before, during, and after Thorazine medication, 5 were much improved, 22 improved, 7 unimproved, and 8 worse. Of 26 inpatients, 4 were much improved, 7 improved, 14 unimproved, and 1 worse. A marked individual variation in dosage was observed in those patients who received Thorazine predominantly orally. With some of the inpatients medication started with intramuscular injections and was later changed to oral doses of Thorazine.

The optimum dosage has to be found for each patient. Some patients need comparatively small amounts and others a fairly high amount of Thorazine. Some patients who receive Thorazine develop an adaptation to the drug, and in such cases the dose has to be increased. Thorazine can be withdrawn rapidly from patients if necessary, and no withdrawal symptoms have been observed. All inpatients were treated on the average of four months, and outpatients were treated about eight months. Practically all our patients showed a return of symptoms when the use of the drug was discontinued. The results in our series were unpredictable. Some patients responded dramatically; others with similar symptoms did not respond at all. Some patients showed only a reduction in their symptoms. In many instances the emotional tension was reduced without the symptoms themselves being removed. This was especially true in psychotic patients, in whom the basic condition remained untouched by the drug.

The paper also discussed the complications occurring with the use of Thorazine. The following side-effects of the drug were observed: rash; double vision; swallowing difficulty; lactation in some female patients; constipation; epigastric pain; hepatitis; a grip-like syndrome, consisting of elevated temperature, joint and muscle pains, nasal stuffiness, dry throat, and malaise, and a typical Parkinsonian syndrome. In addition, we sometimes saw nausea, vomiting, vertigo, diarrhea, and a raising of the convulsive threshold by the drug. Besides the physical side-effects, we also saw psychiatric ones, in which the patient complained of apathy, lassitude, and indecision while under the drug, and at times psychotic manifestations were released in some patients. Some patients complained about unpleasant dreams, and at times uninhibited sexual behavior was observed. It is interesting to note that while most patients feel sedated under the drug, there are a few in whom it creates a great deal of tension and restlessness and a "driveness" is present. All complications which we observed were bothersome but not serious. There were no deaths or other serious complications in our series.

A Controlled Investigation into the Value of Chlorpromazine in the Management of Anxiety States. Dr. Carl Lambert, London, England.

The author gave an account of a controlled therapuetic trial of chlorpromazine in a group of 150 outpatients with anxiety states which he conducted in collaboration with Dr. Linford Rees, consulting psychiatrist, Maudsley Hospital, London. He summarized his findings in the following three points:

1. When the double-blind method and other controlled procedures were utilized, it was found that the results obtained by chlorpromazine were significantly better than with inert tablets.

2. Extended trial with chlorpromazine at optimum dosages resulted in 54% of the group showing marked or moderate symptomatic improvement. Two-thirds of these patients relapsed after a few weeks of clinical improvement despite continued medication with chlorpromazine.

3. This high tendency to relapse, together with the development of side-effects, considerably limits the value of the drug. The usefulness of chlorpromazine in anxiety states would appear to be largely restricted to short-term symptomatic treatment and management.

DISCUSSION

Dr. Herman C. B. Denber: It is indeed a pleasure to discuss these valuable contributions to present-day psychiatry. There is no question in anyone's mind that chlorpromazine has taken a place in the treatment of psychiatric disorders for some time to come. Whether or not this therapy will be the final answer, or only the beginning of the search for the final answer, is another question.

There is complete agreement on Dr. Hoch's indications for chlorpromazine treatment. With respect to the dose, Dr. Hoch advocates a rapid build-up with high doses of chlorpromazine. There is a great controversy at this time between psychiatrists in the United States and those in Europe concerning this question, for the doses used in Europe are far smaller than they are here. I was recently privileged in being able to make a survey of 14 psychiatric hospitals in England, France, and Switzerland to study this question. It became apparent that cultural and psychodynamic factors enter into the content of the psychosis; extremely agitated patients are not usually found in English mental hospitals. The doses used are lowest in Great Britain, and higher in France. It would seem that the clinical effect is proportional to the time-dose ratio. Even with a low dose (150 to 300 mg. daily), if one waits long enough (three to six weeks for acute cases and six to nine months for chronic cases), the desired effect will be achieved. I do not believe that pushing the dose even to 1000 mg. daily in the first few days is any more effective than starting with a low dose and waiting. All that the high dose seems to do is to increase the possibility of side-effects. The results all over Europe have borne this out.

The high incidence of the Parkinson syndrome noted in Dr. Hoch's cases may be attributed (*a*) to the high dose he used or (*b*) to the possibility that he may be dealing with a different patient population than elsewhere.

Dr. Irving S. Dribben, Albany, N. Y.: It may be of interest to mention that we have been working on this problem in Albany. We started in 1953, and we have about 750 cases. The material is chiefly psychiatric, but there is also some neurologic material. I was interested to hear both Dr. Hoch's and Dr. Lambert's papers, and, in general, I would say that up to this time our results would support their findings.

We have never seen a typical, complete Parkinson syndrome. All we have seen is the mask-like facies. Dizziness is a very common symptom, and we have seen jaundice about three times in our series. Our percentage would seem to be less than the figures reported; 3 in 750 would run to less than 0.5%.

I would summarize by saying that it is our feeling at this time that chlorpromazine does have value symptomatically.

DR. PAUL H. HOCH: Dr. Nolan Lewis once remarked that when a new treatment comes out everyone should hurry to use it, because if one does not hurry, very soon the treatment will not be used any more. We have seen this occur repeatedly in psychiatry, and I feel that in this drug we have a little more than a passing therapeutic fancy, but I also feel that this drug will be supplanted rapidly by other compounds which will be more effective and will have fewer side-effects than chlorpromazine itself.

The question arises, and this is important, as to what is the optimum dosage. An optimum dosage does not exist; for each patient it has to be determined individually, and I fully agree that a small dose should be used first and then gradually built up. On the other hand, if you try to build up doses slowly, the patient may develop tolerance to the drug. It is preferable to build up the drug more rapidly in unresponding patients, increasing the dose by 50 mg. daily.

DR. CARL LAMBERT, London, England: I have really nothing to add, except to say that we very much share the conservative attitude that Dr. Hoch adopted.

PHILADELPHIA NEUROLOGICAL SOCIETY AND MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION OF NEUROLOGY AND PSYCHIATRY

Charles Rupp, M.D., *Philadelphia Neurological Society, and*
Harvey H. Ammerman, M.D., *President, Medical Society of the District of Columbia*
Section of Neurology and Psychiatry, Presiding
Joint Meeting, Nov. 5, 1954

Cranial Nerve Palsies Associated with Metastatic Neoplasia of the Meninges. DR. HELENA E. RIGGS, DR. CHARLES RUPP, and DR. HOMER RAY (by invitation), Philadelphia.

The authors reported six cases of cranial nerve syndromes associated with neoplastic involvement of the basal meninges by lymphoma or malignant tumors of the nasopharynx. The cranial nerve symptoms appeared early and dominated the clinical picture. The fifth, sixth, seventh, and eighth nerves were most frequently affected, and signs were often bilateral. The involvement was progressive in most cases but followed no predictable sequence. The syndrome is uncommon, only 6 cases being found in 10,000 necropsies from the neuropathologic laboratory of the Philadelphia General Hospital; but, because of the extreme radiosensitivity of this tumor and the prolongation of life by early therapy, it is important that it be recognized.

DISCUSSION

DR. FRANCIS M. FORSTER, Washington, D. C.: I would like to ask Dr. Riggs whether this neoplasm was present throughout this interval of some five or six years.

In Case 3 I wonder if there is any explanation of the seizures, or whether Dr. Riggs felt that they were perhaps due primarily to involvement of the carotid artery and were therefore on a vascular basis.

While metastases are relatively uncommon in primary intracranial tumors, the cranial nerves may be involved, if you wish to call it metastasis, through the subarachnoid pathways by glial tumors of the central nervous system.

DR. NATHAN S. SCHLEZINGER, Philadelphia: My interest in this group of tumors was aroused by a recent survey of 100 verified brain tumors observed at the Wills Eye Hospital. It was surprising to me that 10 patients were observed in this series with carcinoma of the nasopharynx. In their clinical expression these tumors, of course, are very difficult to diagnose, and in this connection it is important to think of them.

In the group that we have observed at Wills Eye Hospital, the tumors have extended intracranially to involve the anterior group of the cranial nerves, namely, the sixth nerve and nerves anterior to the sixth nerve. There is a group, of course, with involvement of the posterior group of cranial nerves, which by some is felt to be a result of extension extracranially into the region of the jugular foramen.

DR. HELENA E. RIGGS, Philadelphia: Dr. Forster, the interval of six years is correct, and in Clarke's paper there is one case with a 10-year duration. The myelomas are probably as malignant as the nasopharyngeal tumors. As a matter of fact, most of the tumors of the nasopharyngeal type are of the lymphomatous type.

As to the case with the seizures, this man had a definite Stokes-Adams syndrome. He had sudden loss of consciousness with epileptiform seizures and a pulse rate about 40. I am quite sure it was due to pressure of the tumor on the carotid body. After this tumor was removed, we insisted he wear a soft collar. He then had no more seizures.

The fibrosis of the meninges as a cause of cranial nerve symptoms may be a factor, but in our senile cases with a great deal of fibrosis of the leptomeninges we see very little of such involvement and I think we must attribute it to the presence of neoplastic cells. These are scattered throughout the meninges. The nerves are demyelinated, due to the effect of the neoplastic cells blocking the blood supply, rather than involving the nerve fibers per se.

The metastatic lesion involving the optic sheath I have seen only once before, in a meningioma at the base, where the optic nerves were twice their normal size, due to complete obliteration of the fluid pathways by the tumor cells.

It is of interest, also, that the sixth nerve is so frequently involved. Two of our patients were subjected to exploratory operation because of this finding.

Physiological Alterations Following Total Hemispherectomy. DR. F. C. GRANT and DR. G. M. AUSTIN, Philadelphia.

Reports on hemispherectomy of the brain show that total hemispherectomy including the basal ganglia has been done less than a dozen times. We wish to describe our observations on three cases of total hemispherectomy in adults with malignant brain tumor. In one proved case of left-handedness and two of right-handedness, the right hemisphere was completely removed except for the thalamus and a remnant of the central part of the caudate nucleus. All patients remained conscious and speaking throughout the operation. Tendon reflexes recorded oscillographically before and after operation remained unchanged and hyperactive. The Babinski reflex remained positive. Psychological studies showed little, if any, change in intellectual capacity. However, there was increased latency in response to questions, a general decrease in interest and ability to concentrate, and loss of motivation. Within six weeks patients were able to walk either with a cane or supported by one nurse. Pain sensation appeared to be only slightly impaired contralaterally, whereas touch and pressure sensation were markedly diminished. Comparative electroencephalograms showed an increase in amplitude and improvement in normal frequencies from the remaining hemisphere.

These observations suggest the following conclusions:

1. When one hemisphere is badly damaged, there is contralateral inhibition of electrical activity from either injury potentials or desynchronization.

2. Speech localization and handedness do not necessarily involve the same or dominant hemisphere.

3. Full consciousness remains intact with no more than homolateral cortex, basal ganglia, and thalamus.

4. Pain sensation has considerable bilateral representation, whereas touch and pressure have predominantly crossed representation. Further observations and indications were discussed.

DISCUSSION

DR. CLARENCE S. GREENE, Washington, D. C.: It is sometimes more difficult to be critical and analytical than to be creative. Dandy (1929) and Gardner (1939) first reported on hemispherectomy for gliomas. Glioblastoma multiforme was unsuitable because of the frequency of spread through the corpus callosum.

Karnosh (1949) stated that Gardner's patients could walk unaided and could dress themselves. Most hemiplegics can be trained to walk. Hughlings Jackson said that movements of the fingers, which have a most specialized and highly differentiated motor behavior, have the least bilateral cortical control. Gardner reported that no hemiplegic has recovered a useful hand. McKissock and Krynau state that the caudate nucleus should be preserved if volitional control is to return.

The authors concluded, as did Neddles (1942), that speech localization and handedness do not necessarily involve the same or dominant hemisphere. Of interest to the neurosurgeon is which hemisphere is controlling speech preoperatively.

Tinturi's explanation accounts for the absence of hearing loss. The presence of homonymous hemianopsia is generally agreed. I doubt that the seat of consciousness is in the thalamus per se.

The reports all indicate improved behavior, and in most cases a higher I. Q. Dandy and Karnosh disagreed as to epicritic and protopathic sensation. Head and Holmes (1911) indicated that pain was preserved if the thalamus was present.

When one is operating for brain tumor with probable increased intracranial pressure and other vascular changes, it is difficult to tell what structures are actually removed, how much damage is done, and what structures actually remain. This situation could be avoided in infantile hemiplegics—a better group, we think, for physiological study. Is the damage of the association area greater physiologically than the damage done to projection areas? What is the function of the corpus callosum?

DR. ARTHUR KING, Athens, Pa.: I saw one such patient some years ago who had been operated upon by Dr. Dandy. He was much like the one who was shown here. The patient died shortly thereafter; so I cannot say much about him.

I have had experience in two cases. They were children with intractable seizures. The seizures have become less frequent, and the intellect has improved, perhaps because we were able to eliminate the seizures almost entirely with anticonvulsive drugs.

The one patient had previously been taking Dilantin 14 times a day, with phenobarbital in addition, a medication which would make anyone drowsy. Removal of the hemisphere increased the hemiplegia; whereas she could roller-skate before, after the hemispherectomy was done she could not roller-skate. In fact, she needed a brace for her foot to stabilize it, although she does get around quite handily otherwise. However, her hand is now useless. While she is perhaps somewhat happier with the seizures less frequent—they still recur two or three a year—she is certainly more crippled from a physiological standpoint.

DR. G. M. AUSTIN, Philadelphia: As for Dr. Greene's remark on the relation of the thalamus and consciousness, I think I showed you, in the case that came to necropsy, that this total hemispherectomy included the basal ganglia and everything but the thalamus. There followed almost complete degeneration of the thalamus on the side of the hemispherectomy.

Walker obtained total degeneration of all the thalamic nuclei, except the midline nuclei and some of the intralaminar group, in the macaque and the chimpanzee following total hemidecortication with severe damage to the basal ganglia. Our statement was that consciousness requires no more than homolateral cortex, homolateral basal ganglia, and homolateral thalamus, with possibly the exception of the opposite midline and intralaminar nuclei.

The fact that pain sensation was so little affected might again be explained by Walker's observations on the macaque and chimpanzee. There were a number of degenerated areas in the pretectal nuclei and in the midline thalamic nuclei. The midline thalamic nuclei communicate freely, crossing with each other, and this could explain the preserved pain representation.

One could hypothesize that there is an element of plasticity. Eccles defines plasticity as "the ability of synaptic functions to respond appropriately to use and disuse." After hemispherectomy, with its removal of abnormal discharge, the remaining so-called silent cortex perhaps develops much more functional capacity.

Dr. King and Dr. Greene mention improvement in seizures. Again, explanation is difficult without assumptions. First, one assumes that one has removed damaged cortex—not destroyed, but partially damaged, neuronal cortex. Second, many seizures are subcortical rather than cortical in origin. Under those conditions we might say that the two are not mutually exclusive, but that some of the seizure mechanism may be destroyed by degeneration of the thalamic nuclei on the side of the hemispherectomy. Also, removal of the caudate nucleus may be significant, since it has a tremendously important physiological function, having a marked effect on ipsilateral cortical electrical activity when stimulated, and being perhaps the strongest inhibitory subcortical structure.

Thalamic Chronotaraxis. DR. E. A. SPIEGEL, DR. H. T. WYCIS, DR. C. ORCHINIK (by invitation), and DR. H. FREED, Philadelphia.

After bilateral circumscribed lesions in the region of the dorsomedial nuclei, transitory confusion for time (chronotaraxis) was found, frequently alone, sometimes combined with disorientation for place. As a rule, this disturbance lasted only a few days or weeks, but in one case half a year. The patients were confused regarding date, season of the year, and time of the day and showed errors in estimating their age, that of their children, and the duration of their stay in the hospital or their home. Usually the disturbances were associated with memory defects

affecting recent as well as remote events. A constant relationship to anosognosia or to emotional changes could not be established. Sometimes, there was a discrepancy between the patient's feeling as to the passage of time and the judgment of time obtained empirically by intellectual processes. These observations seem to support the view that isolated disturbances of the immediate perception of duration do exist. Various circuits participate in the genesis of the time sense, particularly connections of the dorsomedial nuclei with the frontal lobe and of the anterior nuclei with the mammillary body. The multiplicity of the participating circuits explains that circumscribed lesions of single thalamic nuclei produce only transitory temporal disturbances.

DISCUSSION

DR. JAMES PETER MURPHY, Washington, D. C.: Postmortem examination of the brains of patients exhibiting prominent defects in memory during life has often revealed special pathologic change in the anterodorsal thalamus and the hypothalamus. Disturbances of memory characterize Wernicke's polioencephalitis haemorrhagia and Jakob-Creutzfeldt disease, for example. Loss of commemorative function is usual with disease of the frontal lobes. The effects of dorsomedial thalamotomy, in which discrete and controlled lesions are placed in the thalamus, suggest that the common factor in these disorders is partial destruction of the rostral thalamic nuclei.

It is of interest that Dr. Spiegel and associates have observed impairment of remote as well as of recent memory after dorsomedial thalamotomy. This contrasts with the nonspecific loss of retention and recall found in many types of diffuse cerebral disorders. Foerster and Gagel observed reexperience of memorable events by patients in whom they manipulated the diencephalic region under local anesthesia. Reichert and associates obtained hallucinatory phenomena while stimulating the centromedian thalamus in patients lightly anesthetized.

Loss of memory as a tool is a feature of the postoperative condition of the lobotomized patient. Relief of anxiety after lobotomy may be due simply to loss of fear-producing mental engrams. Dr. Spiegel and Dr. Wycis are to be congratulated upon their demonstration that the normal function of memory, disturbed by a lesion anywhere in the frontal or temporal region of the brain, may be a principal function of the rostral thalamus.

DR. WALTER FREEMAN, Washington, D. C.: It is noteworthy that Dr. Spiegel has been able to reproduce so accurately the phenomena of prefrontal lobotomy by means of small focal lesions in the thalamus.

The effect on the time relationships apparently is of brief duration, except in one case, in which disorientation lasted for a number of months. What other phenomena were present, possibly indicating some more generalized disturbance or an extension of the pathologic process on one side or the other?

I would like to ask Dr. Spiegel a question concerning the biological rhythms of such patients —whether the patients are ready for the next meal at the proper time, whether their sleep rhythms are at all disturbed, and whether their evacuation occurs in more or less normal rhythmical fashion.

Dr. Spiegel has defined temporal disorientation. That, to me, is part of the general syndrome of disorientation, which all psychiatrists are familiar with—person, time, and place. Watts and I added what we think is the most important as far as the lobotomized patients are concerned—the loss of orientation with regard to the self. Dr. Spiegel has mentioned that the patients do not realize they have been operated upon.

Robinson and I have been working on the concept of the continuity of the self, which is possibly part of the larger concept of the self in relation to the self. In other words, we are the same people today as we were yesterday and will be tomorrow. There is a continuation of experience that carries us along from one stage to another.

Something happens to that particular sense of continuity of the self after prefrontal lobotomy. A monograph on this subject will be published soon.

Temporal disorientation may be part of a larger phenomenon of orientation in regard to the self.

DR. E. A. SPIEGEL, Philadelphia: We also stimulated the thalamus in cases in which we operated with local anesthesia; but we were not able to produce definite anxiety, perhaps because we did not apply the proper current. The effect of thalamic lesions upon temporal orientation was much shorter-lasting than that upon the emotional reactions, so that I should doubt whether there is a close connection. There may be some relationship between the chronotaraxis and the ability to concentrate the attention, which Dr. Orchinik found sometimes impaired. Initially,

there was often the lack of spontaneity, of interest in the surroundings; but in the patient in which chronotaraxis existed for about half a year, the memory disturbances were the only other definite signs. With regard to biological rhythms, there was often a prolongation of the sleep periods. It seems quite possible that chronotaraxis may be part of a more general symptom, which chronotaraxis existed for about half a year, the memory disturbances were the only other noticeable symptoms and signs of anosognosia could not be detected. It is quite possible that the disturbances of self-continuity that Dr. Freeman described may be more pronounced in lesions of the frontal lobe, in which not only the frontothalamic but also cerebral association systems are affected.

Clinical Correlates of the Spike Wave Complex. DR. DANIEL SILVERMAN, Philadelphia.

The author examined 2500 consecutive EEG's of neurologic patients, of whom approximately 25% had epileptic seizures, for spike wave complexes; 165 records, representing 154 patients, had such wave forms. Spike waves were divided into classic 3-per-second types (23); other generalized spike waves, varying frequencies, multiple spikes, or slow spikes (63), and focal spike waves, mirror foci, discrete foci, or foci with spread (63). Only three young children did not have seizures prior to this study. In the classic type, petit mal epilepsy was commoner and was best activated by hyperventilation; in the other generalized spike waves, particularly the multiple spike wave, grand mal epilepsy was commoner and was best activated by photic stimulation; in the focal spike waves, focal epilepsy was commoner and was best activated by sleep. Known etiologic factors and positive neurologic signs were rare in the classic group and were progressively commoner in the generalized spike wave and focal spike wave group. This supports the thesis that the classic type represents a "centrencephalic," and the focal a local cortical, discharge, while the other generalized spike waves are mixed types. Activation techniques increased the elicited of spike waves by 47%.

DISCUSSION

DR. HAROLD STEVENS, Washington, D. C.: The organization and analysis of this type of data have given the science of electroencephalography and clinical neurology a new and more balanced concept of the precise and practical meaning of the spike wave formations present in the electroencephalogram of a patient under diagnostic study.

This report negates some of the earlier inferences and confirms the observations of other, more recent reports on the meaning and interpretation of these spike wave patterns. This newer knowledge permits certain useful generalizations, particularly on the part of the clinician who receives the EEG report and who must fit all the facts together.

Spike wave studies, including this one, warrant the following generalizations:

First, the spike wave pattern has a high degree of specificity. I should go a little further. I would say unequivocally that it means epilepsy, either present or future.

Second, spike wave formation does not necessarily mean petit mal epilepsy, as formerly held. In fact, in contrast to the past, when there was insistence on using the term "petit mal pattern" in describing the spike wave formation, this conviction is certainly no longer held, although it is true that in the preponderance of patients with spike wave formations the patient does have petit mal.

Third, the presence of spike wave patterns in the EEG implies that the etiology is most likely idiopathic, but, again, not necessarily so. A wide variety of causes can produce this pattern, some of which Dr. Silverman has already mentioned.

Fourth, a synchronous 3-per-second classic spike wave pattern probably means a centrencephalic origin.

Dr. Silverman's study confirms the work of Penfield and his co-workers and more sharply delineates the study of the spike wave pattern. This more modern position has given emphasis to the clinical history of the patient and the pattern and sequential events of the seizure, rather than to basing the diagnosis and etiology on the EEG pattern exclusively. This development returns the clinical neurologist to the central position in the diagnosis and localization of epilepsy.

Dr. Silverman's contribution, I feel, is a very substantial addition to the expanding science of electroencephalography.

DR. DANIEL SILVERMAN, Philadelphia: I wish to thank Dr. Stevens for his generous comments. I can subscribe to what he says, except that in our experience the multiple spike pattern is more closely correlated with grand mal than with petit mal seizures. We have not had a long enough follow-up on patients to be able to draw any conclusions about the EEG patterns and the prognosis.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

BRAIN AND LIVER PHOSPHORUS METABOLISM IN THE ACUTE RADIATION SYNDROME. W. H. FLORSHEIM and M. E. MORTON, Am. J. Physiol. **176**:15 (Jan.) 1954.

The authors investigated the hypothesis that the "hyperexcitability syndrome" might be mediated through capillary changes, in the form either of destruction or of permeability changes. Previous investigations in acute radiation had revealed no significant microscopic capillary damage or extensive hemorrhages. The present investigation was aimed at a study of changes in capillary permeability, independent of histological changes. In vitro experiments showed no impairment in phosphorus metabolism in irradiated brain tissue. Tracer studies with radiophosphate were undertaken to investigate the alterations in blood-brain barrier which might be reflected by penetration of brain tissue. Radiophosphate was administered peripherally. Mice were used as experimental animals. No significant difference in phosphorus uptake of irradiated mice as compared with that for fasted controls was found. No significant difference in cholinesterase determinations was noted, and a hypoglycemia state was not the cause of the irradiation syndrome. The authors found an "extreme resistance of brain and liver phosphorylative mechanism toward x-irradiation." Histologically, in addition to damage to the subependymal plate, scattered oligodendroglia cells, and neurones, which have been reported previously, these authors also found widespread necrosis among the granular cells of the cerebellum.

BERRY, Silver Spring, Md.

CHEMOSENSITIVITY OF THE RESPIRATORY CENTER: 1. INFLUENCE OF CO_2 IN THE CEREBRAL VENTRICLES ON RESPIRATION. 2. INFLUENCE OF CHANGES IN THE H^+ AND TOTAL BUFFER CONCENTRATION IN THE CEREBRAL VENTRICLES ON RESPIRATION. I. R. LEUSEN, Am. J. Physiol. **176**:39-44 and 45-51 (Jan.) 1954.

In these two papers Leusen reports studies using the technique of perfusion of the cerebral ventricles with various solutions. The fluid entered through the lateral ventricle and left through the cisterna magna. Dogs under morphine-chloralose anesthesia were used—some with intact chemoreceptors, others with denervated carotid sinuses and severed vagus nerves. The author perfused solutions in which changes in CO_2 (or H^+) concentration affected the respiratory centers on the floor of the fourth ventricle. Blood pH varied inversely to the pH changes in the ventricles. It was demonstrated that one influence of CO_2 or H^+ concentration on respiration was due to direct influences on the respiratory centers. Perfusion with increased CO_2 depressed respiratory activity in both those animals with intact and those with denervated chemoreceptors. Respiration was stimulated, both in volume and in amplitude, by increased CO_2 concentration. The influence on respiratory frequency was less marked.

Changes in the pH in the cerebral ventricles independent of changes in the CO_2 concentration failed to influence respiratory activity in animals with denervated chemoreceptors. Leusen concluded that the changes exerted on the respiratory center were due to the CO_2/HCO_3^- ratio rather than to differences in H^+ concentration. The author entertained the possibility that CO_2 and HCO_3^- may be separated by the cell membrane, with the membrane equilibrium the important factor instead of intracellular pH. With use of different buffer concentrations a diphasic reaction was noted. A possible explanation lies in the more rapidly diffusible CO_2, which would thus be present in excess temporarily at the respiratory center.

BERRY, Silver Spring, Md.

EFFECT OF ADRENALECTOMY ON ANTICONVULSANT ACTION OF GLUTAMIC ACID IN MICE. J. L. FULLER and B. E. GINSBURG, Am. J. Physiol. **176**:367 (March) 1954.

Glutamic acid protects DBA/I mice against audiogenic seizures, the protection being greater in males than in females in this strain. It has been suggested that adrenergic action may account for this protection. Fuller and Ginsburg test this hypothesis to determine whether the protective effect is abolished in adrenalectomized animals. It was found in adrenalectomized animals with DCA implants that glutamic acid protection persists.

Ginsburg previously hypothesized that differential susceptibility to audiogenic seizures is a function of genetically controlled metabolic capacities of the CNS. Fuller formulated an hypothesis in terms of the inheritance of an unspecified quantitative character. In the present paper, both authors admit no essential contradiction between these views, since the underlying quantitative variable in the threshold theory may depend upon the efficiency of a specific metabolic system, which may vary from strain to strain. They conclude: "The results of the present experiment are consistent with the hypothesis that genetically controlled differences in seizure susceptibility in one type of mouse are mediated through metabolic differences in the central nervous system, and that the protective effect of glutamic acid may be due to a central rather than a peripheral action."

BERRY, Silver Spring, Md.

EFFECTS OF FLUOROACETATE POISONING ON CITRATE, LACTATE AND ENERGY-RICH PHOSPHATES IN THE CEREBRUM. G. R. PSCHEIDT, D. BENITEZ, L. B. KIRSCHNER, and W. E. STONE, Am. J. Physiol. **176**:483 (March) 1954.

Citric acid accumlates in tissue of fluoroacetate-poisoned animals, in the dog primarily in the CNS. The fluoroacetate is converted to a fluorocitrate, which inhibits the aconitase, thereby blocking the tricarboxylic acid cycle. Morphinized dogs were used in the present experiments, and tissue specimens were obtained after the brain had been frozen in situ. Methylfluoroacetate was injected. After a latency of about 40 minutes, during the preconvulsive period, the brain citrate increased rapidly, to reach a maximum soon after the onset of convulsions. No change in lactate, creatine phosphate, or inorganic phosphate occurred during the preconvulsive period. During the actual convulsive stage lactate increased, and some breakdown of creatine phosphate was apparent, both being regarded as a consequence of the convulsive activity. In the depressed stage following the seizures the electrical and chemical findings resembled extreme anoxia, with lactate very high and with depletion of reverses of phosphate bond energy. Fluoroacetate convulsions are due to neither the blocking of oxidations nor the presence of excess citrate in the brain.

BERRY, Silver Spring, Md.

FORMATION OF AMMONIUM ION IN THE CEREBRUM IN FLUOROACETATE POISONING. D. BENITEZ, G. R. PSCHEIDT, and W. E. STONE, Am. J. Physiol. **176**:488 (March) 1954.

In morphinized dogs ammonium ion concentration increases in the brain during the development of fluoroacetate poisoning. No close relation to ammonium levels is noted in symptoms or in duration of seizures. Blood levels of ammonium are only slightly raised as compared with cerebral levels, which increase over sevenfold, an indication of cerebral origin of ammonium in the brain. The accumulation of ammonium ion precedes that of the citrate. The precursor of the ammonium is not known; neither glutamine nor adenosinetriphosphate appears to play a role, although glutamic acid and aspartic acid are considered as possible in this role. The authors are in agreement with Torda that in pentylenetetrazol seizures the increase in ammonium ion in the brain is a result of excitation rather than its cause. The infusion of ammonium chloride induced cortical seizures in two animals and cortical depression in three animals.

BERRY, Silver Spring, Md.

EFFECTS OF INTRAVENOUS PRISCOLINE ON CEREBRAL CIRCULATION AND METABOLISM. P. SCHEINBERG, I. BLACKBURN, and M. RICH, J. Clin. Invest. **32**:125 (Feb.) 1953.

This study was undertaken in an effort to measure the effects of large doses of intravenous Priscoline on cerebral blood flow, metabolism, and other cerebral metabolic functions in man. Twenty-four patients, chosen from hospital wards, were studied. Most were essentially normal, middle-aged, or elderly persons, and the others had a variety of disease states.

The authors found that intravenous Priscoline, in doses varying from 50 to 100 mg., administered in 15 to 20 minutes, results in an apparent, though not statistically significant, decrease in CBF (cerebral blood flow), an increase in A-VO_2, (cerebral arteriovenous oxygen difference) and A-V GI (cerebral arteriovenous glucose difference); a slight increase in mean arterial pressure; a decrease in arterial CO_2 content and arterial pCO_2; a rise in arterial pH, with no alteration in CMR O_2 (cerebral oxygen consumption), CMR GI (cerebral glucose consumption),

CVR (cerebral vascular resistance), arterial O_2 saturation, arterial pO_2, and cerebral venous pO_2. It is postulated that Priscoline produces mild cerebral vasoconstriction and slight hypoxia of brain tissue, though its effects are variable.

These workers feel that final conclusions concerning the possible efficacy of Priscoline in the treatment of cerebral vascular disease must depend upon carefully controlled clinical observations.

ALPERS, Philadelphia.

EFFECTS OF ACTH ON MENTAL FUNCTION. S. MALITZ, D. A. HOMBURG, and S. MODELL, J. Nerv. & Ment. Dis. **118**:315 (Oct.) 1953.

In order to evaluate the effect of corticotropin on mental function, 11 unselected non-psychiatric patients suffering from infectious hepatitis were studied. All patients received daily an intravenous infusion of dextrose or saline, but some patients, who were known to only one member of the medical staff, also received corticotropin. The dose of corticotropin given I. V. was 20 mg. daily for the first five days, then 10 mg. for the next five days, and 5 mg. thereafter. No gross differences in behavior or affect were observed in the group during the regimen. Psychological tests administered before and during the treatment failed to indicate a significant difference in either the intelligence or the projective tests between the subjects given corticotropin and the control group.

BERLIN, New York.

ADIE'S SYNDROME AND THE ADLER-SCHEIE MECHOLYL TEST. BERTRAM E. SPROFKIN, Neurology **3**:910 (Dec.) 1953.

In 1931 Adie reported a syndrome characterized by a tonic pupillary reaction and the absence of one or more tendon reflexes. In 1940 Adler and Scheie reported on the response of the tonic pupil to weak solutions of methacholine (Mecholyl) chloride instilled in the conjunctival sac. In a series of 11 patients, every tonic pupil constricted with 2.5% methacholine chloride, whereas the normal pupils were unaffected by the drug.

The problem presented by the tonic pupil is its differentiation from the Argyll Robertson pupil of neurosyphilis. When the complete Adie syndrome is present and the deep reflexes are entirely or partly absent, a greater similarity to tabes dorsalis is presented. The author points out that the semidilated tonic pupil, varying in size independently of the lighting, and reacting slowly on near vision and almost imperceptibly to light, should not be confused with the Argyll Robertson pupil. The latter is miotic and constant in size, reacts promptly to near vision, and is rigid to light and irregular in its response to mydriatics. The reaction to methacholine and the normal response of the tonic pupil to mydriatics constitute other distinguishing features.

Three cases are presented, in each of which the Mecholyl test was a simple and helpful aid in differential diagnosis. The first case was one of the many instances in which the Adie syndrome occurs in an emotionally labile woman. The second case was a unique example of the occurrence of a tonic pupil in a patient with amyotrophic lateral sclerosis. The third case was one of late latent syphilis, adequately treated (irreversible serologic test), and Adie's syndrome.

ALPERS, Philadelphia.

THE OPTIC NERVE: PROPERTIES OF A CENTRAL TRACT. P. O. BISHOP, D. JEREMY, and J. W. LANCE, J. Physiol. **121**:415 (Aug.) 1953.

A study of the properties of the fibers of the optic tract in the cat shows that they are all A fibers according to the classification of Erlanger and Gasser (1930) and Gasser and Grundfest (1936). Their conduction velocities range from 30 to 40 m/sec. for the large fibers and from 15 to 23 m/sec. for the smaller fibers. The ratio of conduction velocity (m/sec.) to axonal diameter (μ) is 8.2. The curve of recovery of excitability following activation shows a well-marked phase of supernormality followed by a shallow phase of subnormality. Absolute and relative refractory periods, duration of spike, negative and positive after-potentials, etc., correspond to those of peripheral A fibers.

The correspondence to peripheral A fibers is of interest, since it indicates that the fibers of central nervous system tracts, of which the optic tract is representative, may have the same properties as peripheral nerve fibers.

THOMAS, Philadelphia.

Meninges and Blood Vessels

ACUTE EPIDURAL HEMATOMA IN INFANTS: BRIEF REVIEW AND REPORT OF A CASE. A. C. JOHNSON, A. M. A. Am. J. Dis. Child. **88**:618 (Nov.) 1954.

Johnson reports on a 15-month-old child who had a typical epidural hematoma following trauma, an infrequent occurrence in infants.

SIEKERT, Rochester, Minn.

SALMONELLA MENINGITIS IN INFANCY. E. S. SMITH, A. M. A. Am. J. Dis. Child. **88**:733 (Dec.) 1954.

Smith reviews 16 cases of Salmonella meningitis, in 9 of which the patients recovered. The use of the newer antibiotics appears to have favorably affected the course of this serious and uncommon illness. Chloramphenicol, chlortetracycline, and oxytetracycline appear to be of value.

SIEKERT, Rochester, Minn.

CHRONIC EXTRADURAL HEMATOMAS. W. V. TROWBRIDGE, R. W. PORTER, and J. D. FRENCH, A. M. A. Arch. Surg. **69**:82 (Dec.) 1954.

In contrast to the classic syndrome of acute epidural hemorrhage, the clinical picture of chronic extradural hematoma is uncharacteristic. Chronic extradural bleeding occurs gradually and is presumably venous rather than arterial in origin. The patients complain of increasing headaches for days, or even weeks, following the original injury, but neurologic examination usually fails to demonstrate definite signs. In some cases, however, papilledema and brachycardia may develop. As a rule, the electroencephalogram is of little diagnostic help. Roentgenograms of the skull may or may not show a fracture. The most significant finding is the demonstration of pineal shift, which tends to increase gradually. When this syndrome is observed after head injury, one should not be content with the diagnosis of postconcussional syndrome. The diagnosis of extradural hematoma must be ruled in or ruled out by trephination. Surgical evacuation of the hematoma achieves prompt recovery. It must be admitted that occasionally in a case of chronic extradural hematoma spontaneous resorption may occur, and thus the patient recovers without special treatment. Two illustrative case reports are given.

LIST, Grand Rapids, Mich.

BASILAR ARTERY ANEURYSM. W. E. STERN, Am. J. Roentgenol. **71**:428 (March) 1954.

Stern reports the case of a man who suffered an attack of unconsciousness followed by amnesia and difficulty in talking, swallowing, and breathing about 11 years before the present period of observation. He had been considered well in the interval. Stern saw the patient because of loss of strength in the limbs and a gradual loss of the ability to talk and swallow. Neurologic examination demonstrated that the left palpebral fissure was wider than the right. Swallowing was slow and incomplete. Pharyngeal sensation on the right was impaired. Speech was hoarse, gurgling, wet, and dysarthric. The patient had severe right hemiplegia and mild weakness of the left side.

Plain roentgenograms of the skull showed an oval shadow measuring approximately 3.5 cm. in diameter and located in the midline behind the dorsum sellae and the clivus. There was heavy calcification around the periphery of this oval mass. There was no evidence of bone erosion in the vicinity. An aneurysm of the the basilar artery, a neoplastic cystic tumor, and calcification in normally located thrombotic arteries were considered in the differential diagnosis. Angiograms were obtained by injecting the opaque material into both the vertebral and the common carotid arteries. These studies gave reasonably conclusive confirmation that the calcified lesion was an aneurysm of the basilar artery. The patient has not died and has not been operated upon. The only proof of the diagnosis consists of the roentgenographic findings. The accurate diagnosis of the vascular nature of such a tumor mass in the region of the pons may help one avoid surgical procedures, which are likely to be very dangerous in treatment of this type of lesion.

WEILAND, Grove City, Pa.

NON-INFECTIVE INTRACRANIAL VENOUS THROMBOSIS. H. J. M. BARNETT and H. H. HYLAND, Brain **76**:36 (March) 1953.

Barnett and Hyland report 39 fatal cases of noninfective intracranial venous thrombosis from the Toronto General Hospital, accumulated over a 20-year period. The condition occurred under a variety of circumstances: heart disease (10 cases), including all the common types of myocardial

and valvular disease, the common factors being (with one exception) the presence of right heart failure of severe degree or rapid onset; cachexia and marasmus (7 cases), in which the thromboses seemed only terminal; as a postoperative complication (5 cases), not including craniotomies, sepsis, or cachexia, with thromboses the cause of death in all but 1; as a post-traumatic condition (5 cases), the cases suggesting that a blow might determine the site of the thromboses, but that the altered coagulability of the blood, perhaps brought about by general trauma, was of greater importance; arterial occlusion of hemorrhage (4 cases), as the only observed predisposing factor, in which the arterial lesion was presumed to precede the venous occlusion; postpartum period (3 cases, in which the development of the illness was insidious, assumed to be evidence against an embolic etiology; blood dyscrasias (2 cases); fever therapy and hyperpyrexia (2 cases), and without associated disorder (1 case), perhaps analogous to "pseudotumor cerebri."

Noninfective venous thrombosis is, therefore, much less common intracranially than elsewhere, but it appears that the etiology is the same intracranially as in the veins of the limbus or pelvis, because the thromboses occur under similar circumstances. Almost one-half (18) of the above cases had evidence of thrombosis or embolism elsewhere. The cerebral lesion is characteristically one of hemorrhagic necrosis, superficial or deep or both, often associated with marked subarachnoid hemorrhage, the latter emphasizing the danger of anticoagulant therapy.

If the condition occurs in otherwise healthy persons, e. g., postpartum and with "pseudotumor," recovery is possible. The degree of residua seems to depend on the extent of damage to the subcortical white matter by deep vein thrombosis of extensive hemorrhage following the infarction.

JOHNS, New York.

THE CLINICAL PRESENTATION OF THE CEREBRAL ANGIOMA. I. MACKENZIE, Brain **76**:184, 1953.

MacKenzie presents a review of 50 cases of arteriovenous anomalies. They were supratentorial and intracranial (except one), and represent an incidence of 1% of neurologic admissions. In 16 patients the presenting symptoms was epilepsy, focal in 15 cases, and all had evidence either of a monoparesis or hemiparesis, or a bruit. Of the 15 patients in whom hemorrhage was the presenting symptom, abnormal signs were found in many fewer, and but 1 had a bruit. Related is the fact that angiomas presenting with hemorrhage were somewhat smaller and more deeply placed in the hemispheres than those presenting with epilepsy. All of the 12 patients presenting with headache had a bruit, and 7 of them had "migraine." Two patients with left parieto-occipital angiomas were left-handed but became aphasic as the anomalies manifested themselves, suggesting that such a lesion can bring about dissociation between handedness and speech. In 26 of the 50 cases there was hemorrhage, tending to confirm the feeling that the mortality in hemorrhage from an angioma is substantially less than that from an aneurysm. Presumably, the structure and situation of the angioma make rupture less dangerous, and the development of hemiparesis may, for the same reason, be due to small leaks rather than to relative anemia in the distribution of the middle cerebral artery.

JOHNS, New York.

INFLAMMATORY FACTOR IN PATHOGENESIS OF CEREBROVASCULAR ANEURYSMS. F. P. HANDLER and H. T. BLUMENTHAL, J. A. M. A. **155**:1479 (Aug. 21) 1954.

A controversy has continued for many years as to whether the great majority of intracranial aneurysms develop on the basis of a congenital defect of the medial muscle at points of bifurcation or as the result of arteriosclerosis. During the course of a recent study dealing with sequential morphological changes in the development of arteriosclerosis of basilar arteries, nine instances of a focal arteritis were seen. Such observations motivated a study of the possibility that intracranial aneurysm formation may be a complication of cerebral arteritis.

The nine cases with their pathological findings are described. An apparently heretofore unrecognized pathogenic factor of inflammation in the development of intracranial ("bony") aneurysms was seen in these patients showing various stages of a proliferative arteritis.

From the pathological studies the authors reconstructed a sequential pattern: first, an acute stage of inflammation which progressively involved all layers of the wall and eventually destroyed parts of the internal elastic lamella, and, second, a healed stage in which there are sharply demarcated gaps in the elastica interna and focal fibrous tissue replacement of medial muscle.

The formation of microscopic aneurysms as a complication of this process was also demonstrated. In one case of a clinically demonstrable aneurysm of the anterior communicating artery, an acute proliferative arteritis was discovered in the left middle cerebral artery.

ALPERS, Philadelphia.

ASEPTIC MENINGITIS CAUSED BY COXSACKIE VIRUS WITH ISOLATION OF VIRUS FROM CEREBROSPINAL FLUID. K. HUMMELER, D. KIRK, and M. OSTAPIAK, J. A. M. A. **156**:676 (Oct. 16) 1954.

The authors describe an outbreak of an infection with Coxsackie virus in an institution for mental defectives in which all 11 patients showed clinically an involvement of the central nervous system. From one patient in this series, a Coxsackie virus was isolated from the spinal fluid during the acute stage of illness, and serological evidence is presented showing that this virus caused the aseptic meningitis.

The main feature of this outbreak due to Coxsackie virus Group B is the involvement of the central nervous system in all 11 observed patients. The clinical symptoms were very similar, and the clinical and laboratory data did not contribute to an etiological diagnosis. The spinal fluids showed changes compatible with aseptic meningitis.

A Coxsackie virus was recovered during the acute stage of the illness from five of eight patients studied. From one patient an identical strain was isolated a month after onset, and in two patients the isolation attempts were unsuccessful. Etiologically, the isolation of a Coxsackie virus in the acute stage of illness from the spinal fluid of one patient is the strongest evidence that the isolated Coxsackie virus was the causative agent of the observed syndrome.

The identification and typing of the recovered strains showed that they all belonged to the same group and type of Coxsackie viruses, namely, Group B, Type 2 (Ohio). No other virus strains of the Coxsackie group could be isolated, and evidence of poliomyelitis was absent in the secretions from all patients. The findings in these cases were surprisingly uniform, considering the many variations that may be encountered with Coxsackie viruses, but, as pointed out by these workers, the evidence proves that the Group B viruses, commonly associated with pleurodynia, can invade the central nervous system and cause a benign meningitis that is clinically indistinguishable from the serous meningitis caused by other infectious agents.

ALPERS, Philadelphia.

Diseases of the Brain

ELECTROENCEPHALOGRAPHIC STUDIES OF THE ENCEPHALOPATHIES: III. SERIAL STUDIES IN MEASLES ENCEPHALITIS. L. L. LEVY and E. ROSEMAN, A. M. A. Am. J. Dis. Child. **88**:5 (July) 1954.

The clinical and electroencephalographic findings are reported in 10 cases of measles encephalitis studied by means of serial tracings. It is believed that the presence and duration of the delta activity may be good indicators of the existence of cerebral complications. The presence of slow waves in the electroencephalogram seem either to indicate an acute encephalitis or to be the result of convulsions in close time-relationship to the tracing. Convulsions were seen as initial symptoms in one-half the cases reported. The absence of delta activity is against the diagnosis of active measles encephalitis.

There was a parallelism between the delta activity and the severity of the disease in the acute phase of the illness. The slow waves disappeared with resolution of the acute illness uncomplicated by convulsions. When seizures were present, this seemed to delay the electrical change toward normal. There appeared to be no correlation between the degree and duration of the delta activity during the active phase of the illness and the ultimate prognosis in regard to residual neurologic or mental defects. Also, the severity of the final dysrhythmia bore no relationship to the degree of aberration in mental or behavioral status of the patients studied.

SIEKERT, Rochester, Minn.

NEUROTOXIC SYMPTOMS FOLLOWING INGESTION OF ASTEROL DIHYDROCHLORIDE. C. H. GAY and W. H. JOHNSON, A. M. A. Am. J. Dis. Child. **88**:199 (Aug.) 1954.

Gay and Johnson present the case of a 7-week-old boy with convulsive seizures attributed to the inadvertent ingestion of the antifungal drug Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) hydrochloride.

SIEKERT, Rochester, Minn.

Diseases of the Spinal Cord

PAIN ASSOCIATED WITH ACUTE POLIOMYELITIS: NEUROLOGIC AND THERAPEUTIC CONSIDERATIONS. P. BENDZ, A. M. A. Am. J. Dis. Child. **88**:141 (Aug.) 1954.

From a clinical analysis of a series of patients with poliomyelitis the author observed a close correlation between the site of pain and the motor lesions. From a clinical analysis of the pain there is both a neuralgic and a myalgic element; it is asserted to be of radicular genesis, the neuralgic element being referable to the dorsal roots and the myalgic to the ventral roots. The therapy is symptomatic, and the author advocates caffeine, local hyperemia or anesthesia, and vibration massage.

SIEKERT, Rochester, Minn.

INTRASPINAL TUMORS IN CHILDREN. H. J. SVIEN and H. M. KEITH, J. A. M. A. **155**:959 (July 10) 1954.

This report is based on a review of the clinical records in 41 cases of intraspinal tumor in which the patients were less than 15 years of age. Svien and Keith found that in the majority of cases of intraspinal tumor in children the neoplasm arises from the spinal cord or its envelopes. In 27 (65.9%) of the 41 cases the tumor was of this type. In 9 of the 41 cases the tumor arose in contiguous tissues. In 2 of the 41 cases the intraspinal tumor was a metastatic lesion. The tumor was of the lymphoma type in 2 of the 41 cases.

In reviewing the results of treatment, the authors note that in 14 (34.1%) of the 41 cases, that is, in 8 cases of neurofibroma, 1 case of extradural lipoma, 2 cases of ependymoma of the filum terminale, 2 cases of arachnoid cyst, and 1 case of giant-cell tumor, it could be anticipated that surgical removal of the tumor would result in a cure provided the operation was performed before the tumor had caused irreparable injury of the spinal cord. In 14 of the remaining 27 cases, decompression of the spinal cord or cauda equina could be expected to relieve the symptoms for several months to several years provided the operation was performed before the spinal cord had been injured seriously. The remaining 13 cases of intramedullary tumors of the spinal cord consisted of 6 cases of glioma, 1 case of racemose angioma, 1 case of hemangioendothelioma, and 5 cases of lipoma. If partial removal of the tumor is possible, it sometimes will result in prolonged benefit.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

SYSTEMIC DISEASE AND THE CARPAL TUNNEL SYNDROME. A. W. GROKOEST and F. E. DEMARTINI, J. A. M. A. **155**:635 (June 12) 1954.

Median nerve compression in the volar carpal tunnel (the carpal tunnel syndrome) has been recognized as an effect of trauma and has been ascribed in other reports to the tenosynovitis of rheumatoid arthritis. In this report the authors call attention to the importance of underlying disorders that, in the absence of trauma, may lead to the carpal tunnel syndrome.

The authors describe three patients with the syndrome associated with a systemic disease who came to operation. One had multiple myeloma with amyloid disease; another had primary amyloid disease, and a third had rheumatoid arthritis.

Besides the patient operated on, plasma cell myeloma with amyloid disease and median neuritis were observed in three other patients on whom exploration of the carpal tunnel was not done.

The pertinent clinical findings for these four cases were as follows: The illness began with a median neuritis, which became bilateral in a short time. Diffuse swelling of the first three fingers and a variety of flexion contractures developed. Subcutaneous nodes obviously attached to tendon sheaths were confused with signs of rheumatoid arthritis. A heavy proteinuria was present: The conventional test for Bence Jones protein was positive in two cases. There was no hyperglobulinemia: The highest figure was 2.2 gm. per 100 cc. Myeloma cells were found in the bone marrow of all these patients, and biopsy specimens of tendon sheaths in three instances and tongue nodules in one showed amyloid.

In the experience of these workers the carpal syndrome occurs in rheumatoid arthritis but its incidence is low.

The treatment of the carpal tunnel syndrome is primarily that of decompression. It would seem advisable, on the basis of findings in patients in this report, to perform a biopsy on the tissues for the median nerve compression. Special histological techniques for the demonstration of amyloid are important.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

METABOLIC CRANIOPATHY. H. B. APPELMAN and R. C. MOEHLIG, Am. J. Roentgenol. **71**:420 (March) 1954.

Appelman and Moehlig report two cases of metabolic craniopathy associated with osteopoikilosis in an elderly mother and her middle-aged daughter. Both patients showed increase in thickness of the inner table of the frontal bone in roentgenograms of the skull. Both had multiple sclerotic areas of bone in the spine, giving the appearance of osteopoikilosis. The daughter had similar areas of sclerotic bone in the pelvis. Most writers on osteopoikilosis state that the disease produces no symptoms. Some authors believe that metabolic craniopathy is associated with headaches, fatigue, nervousness, worry, memory defects, dizziness, and an assortment of other symptoms, and that metabolic craniopathy is caused by or associated with dysfunction of the pituitary gland. It appears plausible to Appelman and Moehlig that both metabolic craniopathy and osteopoikilosis may be related in some way to each other and to dysfunction of the pituitary gland.

WEILAND, Grove City, Pa.

RELIABILITY OF BRAIN TUMOR LOCALIZATION BY ROENTGEN METHODS. F. J. HODGES, J. F. HOLT, R. C. BASSETT, and L. J. LEMMEN, Am. J. Roentgenol. **71**:624 (April) 1954.

Hodges has previously reported the effectiveness of roentgenological methods of localization of brain tumors in his department for the years 1931 to 1941. The present report is for the years 1941 to 1951, during which time a slight improvement in accuracy has occurred over the previous series. The use of a more careful clinical neurologic examination, electroencephalograms, and cerebral angiograms probably accounts for the slight increase in accuracy of localization. In the 10-year period which is covered by this report Hodges and his group have performed some form of roentgen examination on 755 patients who were later proved to have a brain tumor by histopathologic examination of tissue. The exact site of the tumor has been demonstrated in these patients either by operation or by autopsy. Correct localization was held to mean a localization which was sufficiently specific to lead the surgeon to open the skull and encounter the tumor through the opening thus made. Localization of a tumor to one or the other cerebral hemisphere was not considered specific enough. Of 803 proved cases the neurologic examination alone produced sufficiently accurate localization in 61%. The electroencephalogram alone produced accurate localization in 22%. Pneumoencephalograms alone produced accurate localization in 60%. Cerebral angiograms alone produced accurate localization in 72%. Ventriculograms alone produced accurate localization in 86%. However, it is not realistic to speak of using these studies alone, for they are always used in conjunction with one another and one type of study is more accurate for particular tumors than another type of study. Thus, some discretion must be used in choosing the study or studies to be applied. A detailed neurologic examination, an electroencephalogram, and plain films of the skull, none of which cause any harm to the patient, were sufficient to localize 73% of the intracranial tumors in this series.

Of the additional methods which can be used, a pneumoencephalogram is usually the least dangerous to the patient. However, this study contributes only about 1% to the 73% accuracy already obtained by the harmless methods. Further accuracy of 4% can be obtained by performing a cerebral angiogram. An accuracy of 78% has now been obtained. A ventriculogram will produce about 20% more accuracy of localization, leaving only about 2% of all intracranial tumors which cannot be localized by a combination of all these methods. Hodges' study done 10 years ago described localization by use of all the present methods except electroencephalography and cerebral angiography. A combination of all the available methods at that time produced a correct localization in 95% of cases. The addition of electroencephalography and cerebral angiography has brought this figure up to 98%. Thus, the electroencephalogram and the cerebral angiogram have contributed only a small part to a method of localization which was very accurate before these methods were introduced. Hodges does not imply that the newer methods are without value. He points out cases in which each can have great value in the diagnosis of brain tumor. A high degree of accuracy in localization can be attained only by selecting from all of the diagnostic methods available by a competent team of physicians.

WEILAND, Grove City, Pa.

News and Comment

GENERAL NEWS

The American Board of Psychiatry and Neurology, Inc.—The following candidates were certified by the American Board of Psychiatry and Neurology, Inc., at a meeting of the Board in New York, December, 1954.

PSYCHIATRY

Alikakos, Louis Chris, Aberdeen, Md.
Alspach, Bruce Walter, Miami, Fla.
Altenberg, Henry Edward, Meriden, Conn.
Alzamora, Elio F., White Plains, N. Y.
Angelos, Peter G., Washington, D. C.
Artiss, Kenneth, L., Phoenixville, Pa.
Asch, Stuart S., New York.
Atkins, Robert W, Rochester, N. Y.
August, Burton, Orangeburg, N. Y.
Ayres, Conrad M., Hudson, N. Y.

Baker, James Love, Pittsburgh.
Bates, Hudson H., Chatham, N. Y.
Berlin, Doris A., New York.
Bernstein, Haskell E., Chicago.
Blass, Gustaf, Stamford, Conn.
Block, Charles L., Fort Leonard Wood, Mo.
Bostian, David William, Ann Arbor, Mich.
Boston, John Armistead, Jr., Philadelphia.
Boyer, Robert S., Philadelphia.
Braun, Eugene J., New York.
Bradley, Nelson John, Willmar, Minn.
Broaddus, Robert Eugene, APO 154, New York.
Brownell, Iverson O., Greenville, S. C.
Bullock, Samuel Carey, Philadelphia.
Burris, B. Cullen, Chicago.
Bushard, Bruce Lauren, San Francisco.

Chlenoff, Simeon O., Orangeburg, N. Y.
Clower, Virginia L., Cambridge, Mass.
Cohn, Werner M., Poughkeepsie, N. Y.
Croft, Perry Dean, Baltimore.

Davis, Ezer H., Pittsburgh.
Dean, Harry Brooks, Norristown, Pa.
DeLawter, Hilbert H., Birmingham, Mich.
del Bosque, Hugo, Arlington, Mass.
Dewald, Paul A., Rochester, N. Y.
Diamond, Oscar K., Willard, N. Y.
Dunton, Harlow Donald, New York.

Eger, William Henry, Newton, Mass.
Egloff, Frank R. L., West Hartford, Conn.
Ennis, Jerome A., New York.
Erskine, Frederick Adams, Linwood, N. J.

Fischer, Abraham B., Brooklyn.
Fischhoff, Joseph, Detroit.
Fitzpatrick, William Norwood, Baltimore.
Folsom, James Cannon, Topeka, Kan.
Foxman, Elliott, Cleveland.

Gaukler, Robert John, Fort Leonard Wood, Mo.
Geer, Frank Densmore, III, New Castle, Pa.
Gelb, Lester A., Fort Knox, Ky.
Goldner, Richard Dan, Northville, Mich.
Goldstein, Norman Philip, Silver Spring, Md.
Gordon, Kenneth Hickok, Jr., Ardmore, Pa.
Gould, Stuart M., Jr., Ann Arbor, Mich.
Goyne, James Bevan, Trenton, N. J.
Griffin, Mark Alexander, Jr., Asheville, N. C.
Gross, Martin, Sykesville, Md.
Grumbles, Lloyd A., Danville, Pa.
Gunter, Martin Julian, Cuyahoga Falls, Ohio.

Hammersley, Donald W., Topeka, Kan.
Hanson, Arthur Merrill, Stockton, Calif.
Harrison, Lyman Lyle, Beverly Hills, Calif.
Harrison, Saul I., Philadelphia.
Harvey, David R. M., Ventura, Calif.
Hayward, Malcolm Lloyd, Philadelphia.
Hubbard, Richmond Chase, Greenwich, Conn.

Ingram, William, Jr., Jacksonville, Fla.

Jensen, Mary-Jane Sophie, Chicago.
Jensen, Viggo W., Detroit.
Johnson, Merlin Hubert, Seattle.

Karush, Aaron, New York.
Kennedy, Timothy V. A., Harrison, N. Y.
Knoff, William Frederick, Syracuse, N. Y.
Kremer, Malvina W., New York.
Krent, Justin, Shaker Heights, Ohio.
Kruchek, Thomas Francis, Park Forest, Ill.
Krupp, George R., Rockville Centre, N. Y.

Lamm, LeRoy Barden, North Little Rock, Ark.
Levy, Robert Isaac, Brooklyn.
Levy, William, Philadelphia.
Lininger, Richard Raymond, Orinda, Calif.
Lubart, Joseph Murray, New York.

Mackenzie, John Munro, Boston.
Magruder, William Wailes, Baltimore.
McPheeters, Harold Lawrence, Schenectady, N. Y.

Mengarini, Ariel Aldace Anteo, New York.
Miller, Jason, New York.
Monke, J. Victor, Los Angeles.
Moore, Kenneth Boyd, Ypsilanti, Mich.
Morris, Elsie M., Montrose, N. Y.

Nemetz, S. Joseph, Cambridge, Mass.

Passoni, John Angelo, New York.
Peck, Harris B., New York.
Peden, James Knox, Dallas, Texas.
Phillips, Philip B., Naval Air Station, Pensacola, Fla.
Pollock, Anthony J., Jr., Indianapolis.

Resnick, Eugene V., New York.
Ring, Floyd O., Omaha.
Ritchie, John C., III, Philadelphia.
Robertson, Raymond Edgar, Hinsdale, Ill.
Robins, Jay K., Brooklyn.
Rond, Philip Chester, Jr., Columbus, Ohio.
Rosen, Joseph D., New York.
Rosenblatt, Allan D., San Diego, Calif.
Rosenzweig, Norman, Ann Arbor, Mich.

Sabbath, Joseph Conrad, Newton, Mass.
Safirstein, Samuel L., New York.
Sandifer, Myron Guy, Jr., Boston.
Saxe, Louis Phillip, New London, Conn.
Schartenberg, Fred Lewis, Cranford, N. J.
Schneller, Leo, New York.
Shapiro, Leon Nathan, Newton Center, Mass.
Sifneos, Peter Emanuel, Belmont, Mass.
Silcott, William Llewellyn, Bronx, N. Y.
Simon, Michael Raymond, New Rochelle, N. Y.
Smith, Thorsten, Chippewa Falls, Wis.
Snyder, Benson Rowell, Boston.
Solow, Robert A., Pacific Palisades, Calif.
Speakman, Walter Fred, Wichita Falls, Texas.
Sprehn, George Warren, Washington, D. C.
Spriegel, William Brooks, Fort Worth, Texas.
Spurlock, Jeanne, Chicago.
Standish, Christopher Thomas, Boston.
Stanton, George T., Chicago.
Stevenson, Robert Benjamin, Columbus, Ohio.
Stoller, Robert Jesse, Los Angeles, Calif.
Strassman, Harvey D., Los Angeles.
Swift, Charles R., Trenton, N. J.

Temeles, Lawrence, Philadelphia.
Texada, Davidson Hargrove, Jr., Augusta, Ga.
Trigg, Harold Leonard, New York.
Trosman, Harry, Camp Pendleton, Oceanside, Calif.
Turk, Richard Errington, Berkeley, Calif.

Vail, David Jameson, Baltimore.
Vieth, Charles Arthur, Columbia, S. C.

Wahl, Charles William, # 3923, FPO, San Francisco.
Ward, Richard Storer, New York.
Washburn, Lawrence L., Jr., Washington, D. C.
Wells, James H., # 3923, FPO, San Francisco.
Westmaas, William John, Birmingham, Mich.
Willig, Doris, Philadelphia.
Wilson, David Hughes, San Francisco.
Wise, Catherine Rachel, Downey, Ill.
Wise, Louis Julius, Cincinnati.
Wood, Howard Page, Philadelphia.

Zheutlin, Abraham, Newark, N. J.
Zimmering, Paul, New York.

SUPPLEMENTARY PSYCHIATRY

Blustein, Herman, Chicago.
Hand, Morton H., Brooklyn.
Lesse, Stanley, New York.
Wilson, William Crosbie, Elgin, Ill.

NEUROLOGY

Cohen, Maynard M., Minneapolis.
Guthrie, Thomas Claiborne, New York.
Hammill, James Francis, Silver Spring, Md.
Horenstein, Simon, Boston.
Jaffe, Robert, New York.
Scheinberg, Peritz, Miami, Fla.
Siekert, Robert George, Rochester, Minn.
Tucker, Jolyon Simeon, Birmingham, Ala.
White, Philip Taylor, Indianapolis.

PSYCHIATRY AND NEUROLOGY

Richardson, Edward Peirson, Jr., Boston.
Weiner, Herbert, Silver Spring, Md.

The American Board of Psychiatry and Neurology, Inc:—The following candidates were certified at a meeting of the Board in New Orleans in March, 1955.

PSYCHIATRY

Adamson, Robert K., Berkeley, Calif.

Barnes, Robert Henry, Durham, N. C.
Barnett, Joseph, Far Rockaway, N. Y.
Betts, Wilmer Conrad, Raleigh, N. C.
Boudwin, James Watson, Orangeburg, N. Y.
Bowling, Lawson Hamilton, Jr., Abington, Pa.
Brockbank, W. Reed, Berkeley, Calif.
Brown, James H., New Orleans.
Carr, Edward Sleight, Livermore, Calif.
Casey, Byron L., Detroit.
Cole, Richard King, Jr., Broomall, Pa.
Constant, George A., Victoria, Texas.
Cooperman, Martin, Washington, D. C.
Craig, James B., Columbus, Ohio
Crudden, Charles H., Phoenix, Ariz.

Davidson, Harold Howard, Detroit
DeBolt, Merlan Edward, New Orleans
Decker, Sam, Downey, Ill.

Edwards, Robert M., Lawrence, Kan.
Engstrom, Denton P., Minneapolis
Evers, Robert N., Norristown, Pa.

Ferguson, Grace Renee, New York
Feuss, Charles David, Jr., Lexington, Ky.
Fierman, Louis B., Hamden, Conn.
Frank, Randolph A., Washington, D. C.

Gatski, Robert L., Danville, Pa.
Gilbert, Michael M., Miami, Fla.
Gilliland, Robert M., Baton Rouge, La.
Glasscock, Thomas Tilden, Denver
Goldstein, Theodore, Hartford, Conn.
Gordon, Gene, Silver Spring, Md.

Haenel, Joachim A., Los Angeles
Hamill, James Edward, Port Arthur, Texas
Harris, David Warner, Washington, D. C.
Hermann, Howard T., Phoenixville, Pa.
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SOCIETY NEWS

American Electroencephalographic Society.—The ninth annual meeting of the American Electroencephalographic Society will take place at the Palmer House, Chicago, on June 10, 11, and 12, immediately preceding the annual meeting of the American Neurological Association. The scientific sessions will be held on Friday afternoon, June 10, 2:00 to 4:15 p. m.; Friday evening, from 8:00 to 10:15 p. m., and Saturday, June 11, from 2:00 to 5:00 p. m.

In addition, there will be two symposia: One symposium, on Microelectrodes, will be held on Saturday, June 11, from 9:30 to 12:00 noon, under the chairmanship of Dr. Herbert H. Jasper. The second symposium, on Clinical EEG Interpretation (Head Injuries), will be held Sunday morning, June 12, from 9:30 a. m. until 12:00 noon, under the chairmanship of Dr. Frederic A. Gibbs.

The annual banquet will take place Saturday, June 11, at 7:30 p. m. Business sessions will take place Friday, June 10, from 4:30 to 6:30 p. m. and 10:30 p. m. to midnight.

Books

Cytoarchitecture of the Human Brain Stem. By Jerzy Olszewski and Donald Baxter, with a foreword by J. Godwin Greenfield. Price, $16.00. Pp. 199. J. B. Lippincott Co., 227-231 S. 6th St., Philadelphia 5, 1954.

The study of the normal cytoarchitecture of the reticular formation was begun at Neustadt in 1945 and concluded at the Montreal Neurological Institute, after expansion of the project to include all of the gray masses of the lower brain stem. Blocks for sectioning were taken from fifteen brain stems (fixed by immersion or perfusion), from the pyramidal decussation to the mammillary bodies. There is first a series of nineteen semischematic cross sections, accompanied by low-power photomicrographs of the same representative levels. The next major part contains descriptions and higher-magnification pictures of the individual nuclei. The sheet size permits reproductions in considerable detail, blurred in physically smaller articles and monographs. The pictures have been beautifully reproduced by Aberegg-Steiner & Cie., A. G., in Berne. Repetition of legends and abbreviations on each spread of the initial atlas is another boon which the large plate size permits.

In the text accompanying the pictures of the nuclei reference is made to function, connections, and pertinent anatomical and physiological literature. It is odd that no references are found to the illustrations of comparative normal and pathologic material from the articles of Baker appearing in the ARCHIVES since 1950. Cranial nerve nuclei are described first, followed by the relay nuclei, and, finally, by the nuclei of unknown connections. In each subdivision, the sequence is caudal-cranial. The lack of an index is partly compensated for by the detailed table of contents; one might have wished at least for pagination on page 16, where there is an alphabetical listing of the nuclei.

This beautifully made atlas will undoubtedly well serve the purposes of the authors in providing a basis for anatomical study, for comparison with abnormal cells, and for correlation in physiological studies with the results obtained in experimental animals.

Prefrontal Leucotomy and Related Operations: Anatomical Aspects of Success and Failure. By A. Meyer and E. Beck. Price, 10s./6d. Pp. 60, with 20 illustrations and 18 tables. Oliver & Boyd, Inc., 98 Great Russell St., London, W. C. 1, 1954.

This is the sort of monograph that takes ten years to write and fifty years to evaluate. Meyer and Beck receive leucotomized brains from all over England and selected 102 for their anatomical study. The other brains came from patients who died too soon for adequate clinical evaluation. The authors are quick to point out that there are many gaps in our knowledge; nevertheless, they have a number of answers to the pressing problems of topical and selective operations on the frontal lobes. Adequate operation is essential; otherwise, relapse is bound to occur. Too extensive operation is followed by severe personality alterations, and sometimes by grave trophic and uremic complications, leading to delayed postoperative death. The cases selected for this study comprised 6 with clinical recovery and 18 with improvement, for comparison with 38 that showed slight improvement and 40 that showed none. The authors divided the frontal lobe into seven segments and three planes: anterior, middle and posterior. In the affective and para-

noid patients there was greater improvement in those patients who had lesions in the ventral, midcentral, and cingulate segments than in those operated upon in the dorsal and dorsolateral segments. However, there was a clear quantitative difference in the number of segments involved in the successful and unsuccessful cases. All the improved patients showed some personality change, but in none was the patient unmanageable. Of all the segments, the midcentral one, containing the thalamofrontal radiation, seemed to be the most important. For good results it was not necessary to sever the ventromedial, orbital, or cingulate area. The authors further point out that both in orbital leucotomy and in bimedial leucotomy there is always involvement of the midcentral segment. The involvement of the lateral and dorsolateral segments was accompanied by more personality change, particularly when there was destruction of wide areas of cortex. The same was true of epilepsy, of which there were 17 cases. The extent of cortical destruction was more important than its location. There was no evidence that the "orbital syndrome," consisting of hyperactivity, euphoria, and apathy, was due to extensive involvement of the orbital areas.

Cingulectomy fails invariably in the major psychoses. It is still under scrutiny in obsessive and epileptic states. Rostral leucotomy "has been abandoned by McKissock because of the disconcerting number of relapses, even in neurotics and mild depressives. . . . In our material, full social recovery was obtained, provided the cut was quantitatively adequate, without consistent involvement of the medial, orbital and cingular segments. This should serve as a deterrent from too atomistic interpretation of frontal lobe function."

This monograph was supported by the William Ramsay Henderson Trust, founded in 1832 "with the provision that a sum of money should be applied by the trustees to the advancement of the Science of Phrenology." How Gall would have greeted this essay!

An Introduction to Physical Methods of Treatment in Psychiatry. Third Edition. By William Sargant and Eliot Slater. Price, 20 s. Pp. 351. E. & S. Livingstone, 16 and 17 Teviot Place, Edinburgh 1, 1954.

The third edition of this standard work has been largely rewritten, particularly the chapter on psychosurgery. There is less emphasis on the abreactive techniques, which found their greatest application in the acute war neuroses. Denis Hill has added a chapter on treatment of the epilepsies that serves to round out the volume in particularly agreeable fashion. Since the publication of the second edition, in 1948, there have been considerable advances, especially in the long-term evaluation of the shock therapies, but chlorpromazine is discussed in two pages, and reserpine does not appear in the index. The writing is forceful without being dogmatic. The authors show great versatility in the management of patients, shifting from one method to another, and back again, in accordance with the changing clinical picture of the disease. The patient is thus given the widest latitude in therapy in order to hasten recovery. "The good clinician will avoid set courses of treatment."

The number of remedies that are effective under given conditions is now so large that the therapist must keep on his toes. The authors are particularly severe in their stricture of psychiatrists who give electroconvulsive shock therapy indiscriminately. There are so many bad results, especially in the elderly, and the conversion of so many apparently benign depressions into unmanageable psychoses, that the sounding of a note of caution seems warranted. The various methods are described in considerable detail, their indications and contraindications, their complications, and their stability. All this is of importance to the therapist who would get the best out of the resources at his command.

As far as leucotomy is concerned, the authors conclude as follows: "For too long leucotomy has been considered a last desperate recourse, the failure of which means the end of all hope. Neither the one view nor the other is justified. The consideration of a modified leucotomy should not be postponed till the patient's state is desperate; and if it fails there may still be much to be done. One of our patients had fifteen years, on and off, of psychoanalysis for an atypical obsessional state, before being subjected to a modified operation. Paranoid and depressive symptoms then emerged, necessitating insulin coma and E. C. T. The persistence of tension, despite partial relief of other symptoms, then led to a second operation, after which more E. C. T. was called for. Since that time the patient has been kept out of hospital by daily attendance at an out-patient clinic, occupational therapy and periodic intravenous acetylcholine treatment which have helped her to cope with her residual incapacities. . . . Therapeutic persistence in the face of what may seem overwhelming initial difficulties is a duty which the psychiatrist cannot evade."

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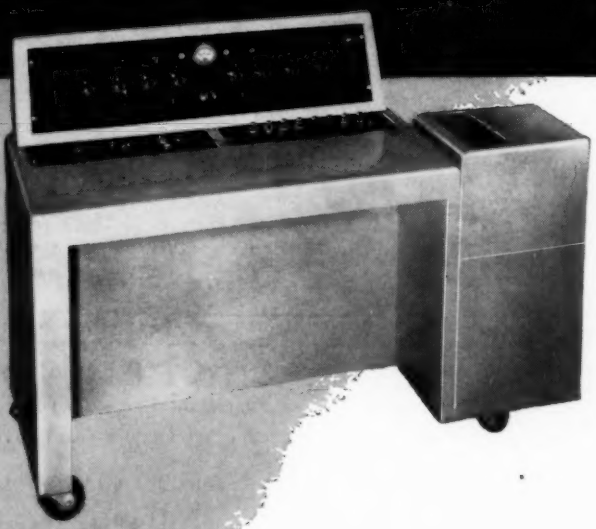

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